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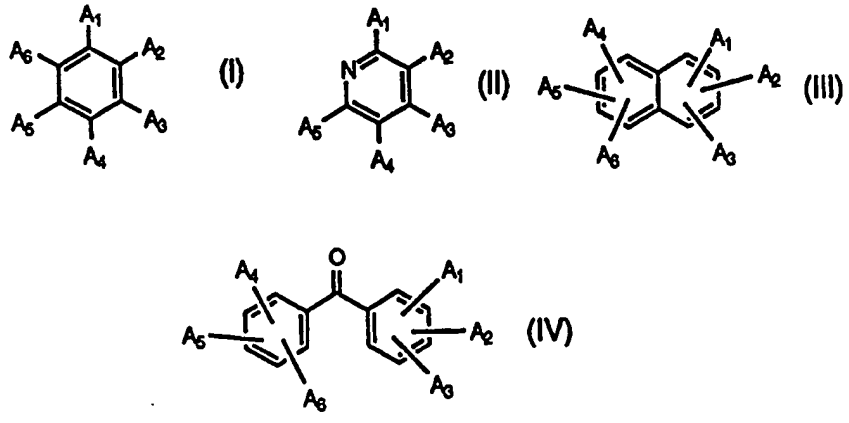

(57) Abstract

The present invention provides a compound of formula (I), (II), (III) or (IV), processes for the preparation of the compounds of the invention, intermediates useful in these processes, a pharmaceutical composition, and methods of using the compounds of the invention.

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BENZENE, PYRIDINE, NAPHTALENE OR BENZOPHENONE DERIVATIVES AS INHIBITORS OF SQUALENE SYNTHETASE AND PROTEIN FARNESYLTRANSFERASE

This is a continuation-in-part of U.S. patent application Serial No. 08/429,095, filed May 3, 1995, which is a continuation-in-part of U.S. patent application Serial No. 322,783, filed October 18, 1994, which is a continuation-in-part of U.S. patent application Serial No. 289,711, filed August 12, 1994, which is a continuation-in-part of U.S. patent application Serial No. 147,708, filed November 4, 1993.

Technical Field

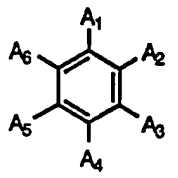
The present invention relates to new cyclobutane dicarboxylic acid compounds which are useful in inhibiting *de novo* squalene production or inhibiting protein farnesyltransferase and the farnesylation of the oncogene protein Ras or inhibiting fungal growth and to chemotherapeutic, antifungal, hypolipidaemic and antiatherosclerotic compositions containing such compounds and to a method of using such compounds for inhibiting cholesterol biosynthesis and atherosclerosis, for inhibiting protein farnesyl-transferase and the farnesylation of the oncogene protein Ras and as antifungals.

Background of the Invention

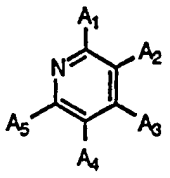
Squalene synthetase is a microsomal enzyme which catalyzes the reductive dimerization of two molcules of farnesyl pyrophosphate (FPP) in the presence of nicotinamide adenine dinucleotide phosphate, reduced form, (NADPH) to form squalene (Poulter, C. D., Rilling, H. C., in "Biosynthesis of Isoprenoid Compounds", Vol. I, Chapter 8, pp. 413-441, J. Wiley and Sons, 1981 and references therein). This enzyme is the first committed step of the *de novo* cholesterol biosynthetic pathway. Thus inhibition of squalene synthetase will lead to inhibition of cholesterol biosynthesis and thus will act as a hypocholesterolemic. Thus squalene synthetase inhibitors ultimately should be useful for the treatment and prevention of hyperlipidaemia or atherosclerosis or other disorders resulting from an excess of cholesterol.

Disclosure of the Invention

In accordance with the present invention there are provided compounds of the formula (I), (II), (III) and (IV):



(I),



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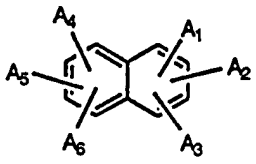
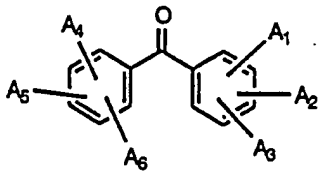


(III),



(IV)

wherein

A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from the group consisting of

(1) hydrogen;
(2) halogen;
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) -X-T-G

wherein at each occurrence T is independently selected from the group consisting of

a) a covalent bond,
b) -C(O)-,
c) -C(S)- and
d) $-S(O)_2-$,

at each occurrence X is independently selected from the group consisting of

a) a covalent bond,
b) $-CH_2-$,
c) -O-,
d) -S- and
e) $-N(R_a)-$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl,

and at each occurrence G is independently selected from the group consisting of

a) R_2 ,
b) $-N(R_1)(R_2)$
wherein at each occurrence R_1 is independently selected from the group consisting of
(i) $-CH(R_d)C(O)OR_e$ wherein at each occurrence R_d is independently selected from the group consisting of loweralkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, thioalkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, arylalkyl and alkylsulfonylalkyl and at each occurrence R_e is independently selected from the group consisting of hydrogen and carboxy-protecting group,
(ii) aryl,
(iii) arylalkyl,
(iv) heterocyclic,
(v) (heterocyclic)alkyl,
(vi) cycloalkylalkyl and
(vii) aryl, heterocyclic, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the aryl part of the arylalkyl group, the heterocyclic group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with one or two substituents $-W-R_4$ wherein at each occurrence W is independently selected from the group consisting of (a) a covalent bond, (b) $-C(O)-$, (c) $-CH_2-$, (d) -O-, (e) $-S(O)_p-$

wherein p is 0, 1 or 2, (f) -N(R_c)- wherein R_c is hydrogen or loweralkyl, (g) -CH_2O-, (h) -$CH_2S(O)_p$- wherein p is 0, 1 or 2 and (i) -$CH_2N(R_c)$- wherein R_c is hydrogen or loweralkyl

and

at each occurrence R_4 is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl,

and

at each occurrence R_2 is independently selected from the group consisting of
(i) aryl,
(ii) arylalkyl,
(iii) alkenyl,
(iv) alkynyl,
(v) arylalkenyl,
(vi) arylalkynyl,
(vii) (heterocyclic)alkyl,
(viii) aryloxyalkyl,
(ix) aryloxyalkenyl,
(x) arylalkoxyalkenyl,
(xi) arylalkyl wherein the alkyl group is substituted with (a) -OR_{10} wherein R_{10} is hydrogen or alkanoyl or (b) -$C(O)OR_h$ wherein R_h is hydrogen or a carboxy-protecting group,
(xii) aroyloxyalkyl, and
(xiii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with one or two substituents -Y-R_3 wherein at each occurrence Y is independently selected from the group consisting of (a) a covalent bond, (b) -C(O)-,

(c) $-CH_2-$, (d) -O-, (e) $-S(O)_m-$ wherein m is 0, 1 or 2, (f) $-N(R_b)-$ wherein R_b is hydrogen or loweralkyl, (g) $-CH_2O-$, (h) $-CH_2S(O)_m-$ wherein m is 0, 1 or 2 and (i) $-CH_2N(R_b)-$ wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl,

and

c) $-NHR_{2a}$ or $-OR_{2a}$
wherein at each occurrence R_{2a} is independently selected from the group consisting of

(i) arylalkyl and

(ii) heterocyclicalkyl,

wherein the alkyl part of the arylalkyl group or the heterocyclicalkyl group is substituted with an arylalkyl group and wherein the aryl part of the arylalkyl group or the heterocyclic part of the heterocyclicalkyl group is substituted with one or two substituents $-Y'-R_{3'}$ wherein at each occurrence Y' is independently selected from the group consisting of (a) a covalent bond, (b) -C(O)-, (c) $-CH_2-$, (d) -O-, (e) $-S(O)_{m'}-$ wherein m' is 0, 1 or 2, (f) $-N(R_{b'})-$ wherein $R_{b'}$ is hydrogen or loweralkyl, (g) $-CH_2O-$, (h) $-CH_2S(O)_{m'}-$ wherein m' is 0, 1 or 2 and (i) $-CH_2N(R_{b'})-$ wherein $R_{b'}$ is hydrogen or loweralkyl and at each occurrence $R_{3'}$ is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;

(7) -Z wherein at each occurrence Z is independently selected from the group consisting of

a) -Q-D

wherein at each occurrence D is independently selected from the group consisting of

(i) $-C(O)R_6$ wherein at each occurrence R_6 is independently selected from the group consisting of hydrogen and a carboxy-protecting group,

(ii) -C(O)H,

(iii) $-CH_2OH$,

(iv) $-C(O)CF_3$,

(v) $-CH(OH)CF_3$,

(vi) $-C(OH)(CF_3)_2$,

(vii) $-C(O)NH_2$,

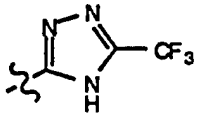
(viii) -C(O)NHOH,

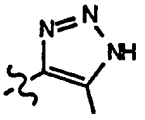
(ix) -CH(=NOH),

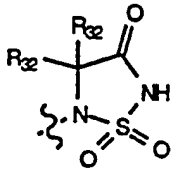
(x) $-S(O)_2NH_2$,

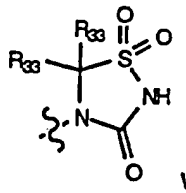
(xi) $-NHS(O)_2CH_3$ or $-NHS(O)_2CF_3$,

(xii) 5-tetrazolyl,

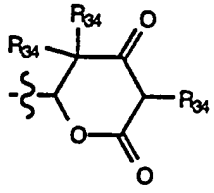
(xiii)  ,

(xiv)  wherein R_{30} is -CN, $-NO_2$, or $-CO_2R_{31}$ wherein R_{31} is hydrogen, aryl or loweralkyl,

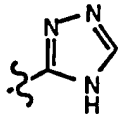
(xv)  wherein at each occurrence R_{32} is independently selected from the group consisting of hydrogen and loweralkyl,



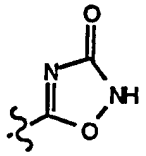
(xvi) wherein at each occurrence R_{33} is independently selected from the group consisting of hydrogen and loweralkyl,



(xvii) wherein at each occurrence R_{34} is independently selected from the group consisting of hydrogen, loweralkyl, alkenyl, alkoxyalkyl and benzyl,



(xviii) ,



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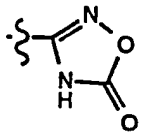

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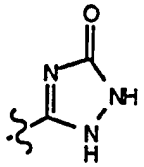

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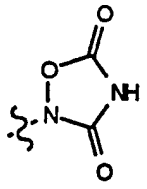
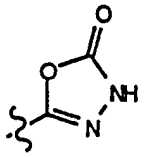
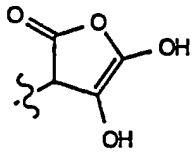
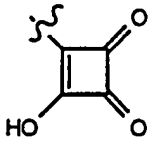
(xxii)  ,

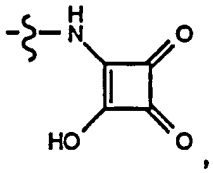
(xxiii)  ,

(xxiv)  ,

(xxv)  ,

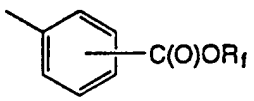
and

wherein at each occurrence Q is independently selected from the group consisting of (i) a covalent bond, (ii) $-OCH_2-$, (iii) alkylene, and (iv) alkenylene;

b)  ,

and

c)



wherein at each occurrence R_f is independently selected from the group consisting of hydrogen and a carboxy-protecting group;

(8) $-C(O)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above;

(9) $-CH(OH)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above;

(10) $-CH=C(R_{2b})(R_{2c})$ wherein at each occurrence R_{2b} is independently selected from arylalkyl and at each occurrence R_{2c} is independently selected from the group consisting of aryl and heterocyclic wherein the aryl or heterocyclic ring is subsubstituted with $-Y'-R_{3'}$ wherein at each occurrence Y' and $R_{3'}$ are independently defined as above,

(11) $-C(O)-CH(R_{2a})CH(R_{2d})C(O)OR_g$ wherein at each occurrence R_{2a} is independently defined as above, at each occurrence R_{2d} is independently selected from aryl and at each occurrence R_g is independently selected from the group consisting of hydrogen and a carboxy-protecting group;

and

(12) -C(O)NH(arylalkyl);

or any two adjacent substituents selected from A_1, A_2, A_3, A_4, A_5 and A_6 taken together form a 5-, 6- or 7-membered cyclic anhydride group;

with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is independently selected from the group consisting of

(1) -X-T-G wherein at each occurrence X, T and G are independently defined as above,

(2) $-C(O)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above,
(3) $-CH(OH)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above,
(4) $-CH=C(R_{2b})(R_{2c})$ wherein at each occurrence R_{2b} and R_{2c} are independently defined as above,
and
(5) $-C(O)-CH(R_{2a})CH(R_{2d})C(O)OR_g$ wherein at each occurrence R_{2a}, R_{2d} and R_g are independently defined as above,

and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is -Z which at each occurrence is independently defined as above;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of the invention are compounds of formula (I), (II), (III) or (IV) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from
(1) hydrogen,
(2) halogen,
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) heterocyclic, (iv) (heterocyclic)alkyl and (vi) R_2, and at each occurrence R_2 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) alkenyl, (iv) alkynyl, (v) arylalkenyl, (vi) arylalkynyl, (vii) (heterocyclic)alkyl, (viii) aryloxyalkyl, (ix) aryloxyalkenyl, (x) arylalkoxyalkenyl, (xi) arylalkyl wherein the alkyl group is substituted with $-OR_{10}$ wherein R_{10} is hydrogen or alkanoyl, and (xii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group

is substituted with -Y-R_3 wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) -C(O)-, (c) -CH_2-, (d) -O-, (e) -$S(O)_m$- wherein m is 0, 1 or 2, (f) -$N(R_b)$- wherein R_b is hydrogen or loweralkyl, (g) -CH_2O-, (h) -$CH_2S(O)_m$- wherein m is 0, 1 or 2 and (i) -$CH_2N(R_b)$- wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;
and
(7) -Q-$C(O)R_6$ wherein at each occurrence Q is independently selected from (a) a covalent bond, (b) alkylene, and (c) alkenylene and R_6 is -OR_7 wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is -$C(O)NR_1R_2$, -$N(R_a)$-$C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, -O-$C(O)NR_1R_2$ or -CH_2-$C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is -Q-$C(O)R_6$ wherein Q and R_6 are as defined above.

More preferred compounds of the invention are compounds of formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from
(1) hydrogen,
(2) halogen,
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) -$C(O)NR_1R_2$, -$N(R_a)$-$C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, -O-$C(O)NR_1R_2$ or -CH_2-$C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) heterocyclic, (iv) (heterocyclic)alkyl and (vi) R_2, and at each occurrence R_2 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) alkenyl, (iv) alkynyl, (v) arylalkenyl, (vi) arylalkynyl, (vii) (heterocyclic)alkyl,

(viii) aryloxyalkyl, (ix) aryloxyalkenyl, (x) arylalkoxyalkenyl, (xi) arylalkyl wherein the alkyl group is substituted with $-OR_{10}$ wherein R_{10} is hydrogen or alkanoyl, and (xii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with $-Y-R_3$ wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) -C(O)-, (c) $-CH_2-$, (d) -O-, (e) $-S(O)_m-$ wherein m is 0, 1 or 2, (f) $-N(R_b)-$ wherein R_b is hydrogen or loweralkyl, (g) $-CH_2O-$, (h) $-CH_2S(O)_m-$ wherein m is 0, 1 or 2 and (i) $-CH_2N(R_b)-$ wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;

and

(7) $-Q-C(O)R_6$ wherein at each occurrence Q is independently selected from (a) a covalent bond, (b) alkylene, and (c) alkenylene and R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;

with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-Q-C(O)R_6$ wherein Q and R_6 are as defined above.

Even more preferred compounds of the invention are compounds of formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from

(1) hydrogen,

(2) halogen,

(3) loweralkyl;

(4) hydroxy;

(5) alkoxy;

(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or

$-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from (i) arylalkyl, (ii) (heterocyclic)alkyl and (iii) R_2, and at each occurrence R_2 is independently selected from (i) arylalkyl, (ii) arylalkenyl, (iii) aryloxyalkyl, (iv) aryloxyalkenyl, (v) arylalkoxyalkenyl, and (vi) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with $-Y-R_3$ wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) $-CH_2-$, and (c) -O- and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) heterocyclic and (d) (heterocyclic)alkyl;
and
(7) $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;
with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)R_6$ wherein R_6 is as defined above.

Even more highly preferred compounds of the invention are compounds of formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from
(1) hydrogen,
(2) halogen,
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from benzyl, 2-ethoxybenzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and
4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl, 3-(4-methylphenoxy)benzyl, and 4-(phenoxy)phenethyl; and

(7) $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;
with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)R_6$ wherein R_6 is as defined above.

Most preferred compounds of the invention are compounds of formula (I) wherein A_1 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 is selected from benzyl, chlorobenzyl, 2-ethoxybenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and R_2 is selected from 4-(phenoxy)benzyl, 3-(4-methylphenoxy)benzyl, and 4-(phenoxy)phenethyl;
A_2, A_4 and A_5 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; or A_3 and A_4 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; or A_2 and A_4 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen.

Most preferred compounds of the invention also are compounds of formula (I) wherein A_1 and A_4 are $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from benzyl, chlorobenzyl, dichlorobenzyl, 2-ethoxybenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl,

3-(4-methylphenoxy)benzyl, and 4-(phenoxy)phenethyl; and A_2 and A_5 are R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen;

or A_1 and A_5 are $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from benzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl and 4-(phenoxy)phenethyl; and A_2 and A_4 are R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen.

The present invention also relates to processes for preparing the compounds of formula (I), (II), (III) and (IV) and to the synthetic intermediates useful in such processes.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of the present invention in combination with a pharmaceutically acceptable carrier.

In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of the present invention in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting protein farnesyltransferase in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound of the invention.

In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

In yet another aspect of the present invention is disclosed a method for treating or preventing restenosis in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound of the invention.

The compounds of the invention comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30.

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo*, for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 loweralkyl (e.g., methyl, ethyl or tertiary

butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxycarbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl,

benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{85}C(O)$- wherein R_{85} is a loweralkyl group.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{86}-NH- wherein R_{86} is an alkanoyl group.

The term "alkanoyloxy" as used herein refers to $R_{87}C(O)$-O- wherein R_{87} is a loweralkyl group.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group.

The term "alkenyl" as used herein refers to a branched or straight hydrocarbon chain comprising two to twenty carbon atoms which also comprises one or more carbon-carbon double bonds. Representative alkenyl groups include 2-propenyl (i.e., allyl), 3-methyl-2-butenyl, 3,7-dimethyl-2,6-octadienyl, 4,8-dimethyl-3,7-nonadienyl, 3,7,11-trimethyl-2,6,10-dodecatrienyl and the like.

The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include -CH=CH-, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CHCH_2-$, and the like.

The term "alkoxy" as used herein refers to RO- wherein R is a loweralkyl group. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like.

The term "alkoxyalkoxy" as used herein refers to $R_{80}O$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is an alkylene group. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl radical as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{96}-C(O)-O- wherein R_{96} is an alkoxyalkyl group.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxylcarbonyl group as previously defined appended to a loweralkyl radical. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{97}-NH- wherein R_{97} is an alkoxycarbonyl group.

The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{93}-O- wherein R_{93} is an alkoxycarbonyl group.

The term "alkylamino" as used herein refers to $R_{51}NH$- wherein R_{51} is a loweralkyl group, for example, methylamino, ethylamino, butylamino, and the like.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{98}-C(O)-NH- wherein R_{98} is an alkylamino group.

The term "alkylsulfonyl" as used herein refers to $R_{82}S(O)_2$- wherein R_{82} is a loweralkyl group.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group.

The term "alkynyl" as used herein refers to a branched or straight hydrocarbon chain comprising two to twenty carbon atoms which also

comprises one or more carbon-carbon triple bonds. Representative alkynyl groups include ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

The term "amino" as used herein refers to $-NH_2$.

The term "aminoalkyl" as used herein refers a loweralkyl radical to which is appended an amino group.

The term "aroyloxyalkyl" as used herein refers to an alkyl radical which is substituted with $R_{20}C(O)-O-$ where R_{20} is an aryl group. Examples of aroyloxyalkyl groups include benzoyloxymethyl, 1-naphthoyloxymethyl, 2-naphthoyloxymethyl and the like.

The term "aryl" as used herein refers to a mono-, bi- or tricyclic carbocyclic ring system comprising 6-14 carbon atoms and having one, two or three aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, anthracenyl, dihydroanthracenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an aryl group as previously defined appended to an alkenyl radical as previously defined. Examples of arylalkenyl include styryl (*i.e.*, 2-phenylethenyl), 2-(1-naphthyl)ethenyl and the like.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{95}-O-C(O)-O-$ wherein R_{95} is an arylalkenyl group.

The term "arylalkoxy" as used herein refers to $R_{84}O-$ wherein R_{84} is an arylalkyl group.

The term "arylalkoxyalkenyl" as used herein refers to an alkenyl radical to which is appended an arylalkoxy group.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{91}C(O)O$- wherein R_{91} is an arylalkyl group).

The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{92}-O-C(O)-O- wherein R_{92} is an arylalkyl group.

The term "arylalkynyl" as used herein refers to an alkynyl radical to which is appended an aryl group.

The term "aryloxy" as used herein refers to $R_{83}O$- wherein R_{83} is an aryl group.

The term "aryloxyalkenyl" as used herein refers to an alkenyl radical to which is appended an aryloxy group.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{94}-O-C(O)-O- wherein R_{94} is an aryl group.

The term "aryl-substituted cycloalkylalkyl" as used herein refers to a cycloalkylalkyl radical in which the alkyl portion of the radical is substituted with an aryl group. Examples of aryl-substituted cycloalkylalkyl include α-(cyclopropylmethyl)benzyl, α-(cyclobutylmethyl)benzyl and the like.

The term "carboxaldehyde" as used herein refers to the group -C(O)H.

The term "carboxamide" as used herein refers to the group $-C(O)NH_2$.

The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy (-COOH) group.

The term "cycloalkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyloxy group (i.e., R_{88}-C(O)O- wherein R_{88} is a cycloalkyl group).

The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like.

The term "cycloalkyloxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended R_{89}-O-C(O)- wherein R_{89} is a cycloalkyl group.

The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{90}-O-C(O)-O- wherein R_{90} is a cycloalkyl group.

The term "dialkylamino" as used herein refers to $R_{56}R_{57}N$- wherein R_{56} and R_{57} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like.

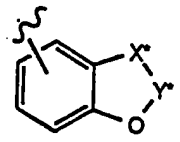
The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group.

The term "dialkyaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended R_{99}-C(O)- wherein R_{99} is a dialkylamino group.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms

and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl. Heterocyclics also include compounds of the formula  where X* is $-CH_2-$ or -O- and Y* is -C(O)- or $[-C(R'')_2-]_v$ where R" is hydrogen or C_1-C_4-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -COOH, $-SO_3H$ and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{100}-C(O)-O- wherein R_{100} is a heterocyclic group.

The term "heterocyclic-substituted cycloalkylalkyl" as used herein refers to a cycloalkylalkyl radical in which the alkyl portion of the radical is substituted with a heterocyclic group. Examples of heterocyclic-substituted cycloalkylalkyl include α-(cyclopropylmethyl)furan-2-ylmethyl, α-(cyclobutylmethyl)thien-2-ylmethyl and the like.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended a hydroxy (-OH) group.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like.

The term "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl radical as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like.

Preferred compounds of the invention are selected from the group consisting of:

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid;

2,5-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,4-dicarboxylic acid;

4,6-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,3-dicarboxylic acid;

5-[N-Phenethyl-N-(4-phenoxybenzyl)diaminocarbonyl]benzene-1,2,4-tricarboxylic acid;

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid;

5-[N,N-Di(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid;

5-[N-(4-Phenoxybenzyl)-N-(4-phenylbutyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid;

5-[N-(3,4-Dichlorobenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid;

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid;

5-[N-Benzyl-N-(2-(4-phenoxyphenyl)ethyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid;

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}benzene-1,2-dicarboxylic acid;

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]oxy}benzene-1,2-dicarboxylic acid;

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methyl}-1,2-benzene dicarboxylic acid; and

5-[N-(2-Ethoxybenzyl)-N-(3-(4-methylphenoxy)benzyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid;

or a pharmaceutically acceptable salt thereof.

Particularly preferred is the compound 5-[N-(2-Ethoxybenzyl)-N-(3-(4-methylphenoxy)benzyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid, or a pharmaceutically acceptable salt thereof.

In general, the compounds of the invention can be prepared by the processes illustrated in Schemes I-VIII. In the schemes, the preparation of compounds of the formula (I) are shown as representative examples. Similar methods can be applied to the preparation of compounds of the formula (II), (III) and (IV).

According to reaction Scheme I, 1,2,4,5-benzenetetracarboxylic dianhydride in an inert solvent such as acetone and acetonitrile or toluene is treated with one equivalent of HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in the presence of an aprotic base such as triethylamine or diisopropylethylamine followed by hydrolysis of the second anhydride (for example, using hydrochloric acid in methylene chloride) gives amide 2.

Compound 3 in an inert solvent such as THF in the presence of an aprotic base such as triethylamine can be reacted with one equivalent of HNR_1R_2 (where R_1 and R_2 are as defined previously herein), followed by hydrolysis of the anhydride (for example, using hydrochloric acid in methylene chloride), to give amide 4. Other substitution patterns can be obtained starting from the appropriately substituted mono- or dianhydrides.

Phthalic anhydride 5 can be reacted with HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in toluene in the presence of an aprotic base such as triethylamine to give mono-amide mono-carboxylic acid 6. Other substitution patterns can be obtained starting from the appropriately substituted mono- or dianhydrides.

The preparation of compounds having a 2,5- or 2,4-diamide substitution pattern is shown in Scheme II. Treating 1,2,4,5-benzenetetracarboxylic dianhydride (1) in an inert solvent such as acetone and acetonitrile or toluene with greater than 2 equivalents of HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in the presence of an aprotic base such as triethylamine or diisopropylethylamine, followed by hydrolysis of the second anhydride (for example, using hydrochloric acid in methylene chloride) when only one anhydride reacts, gives a mixture of amide 2 and diamides 10 and 11 which are separable by column chromatography.

The preparation of compounds having a 1,3- or 1,4-dicarboxylic mono-amide substitution pattern is shown in Scheme III. Treating 1,2,4-benzenetricarboxylic anhydride (12) in an inert solvent such as acetone and acetonitrile or toluene with one equivalent of HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in the presence of an aprotic base such as triethylamine or diisopropylethylamine affords mono-amide dicarboxylic acids 13 and 14 which are separable by column chromatography.

The preparation of compounds having a 1,2- or 1,3-dicarboxylic acid mono-amide substitution pattern is shown in Scheme IV. Treating 1,2,3-benzenetricarboxylic anhydride (15) in an inert solvent such as acetone and acetonitrile or toluene with one equivalent of HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in the presence of an aprotic base such as triethylamine or diisopropylethylamine affords mono-amide dicarboxylic acids 16 and 17 which are separable by column chromatography.

The preparation of compounds having a 1,3-dicarboxylic acid 5-amide substitution pattern is shown in Scheme V. Benzene-1,3,5-tricarboxylic acid triester (18) (wherein R is loweralkyl) in a solvent system such as methanol and THF is treated with one equivalent of a base such as potassium hydroxide or lithium hydroxide to give the mono-carboxylic acid diester 19. The carboxylic acid functionality is activated (for example by treatment with oxalyl chloride) to give compound 20 (wherein X' is a leaving group such as chloro). The activated acid (20) is then reacted with HNR_1R_2 (where R_1 and R_2 are as defined previously herein) in the presence of an aprotic base such as triethylamine or diisopropylethylamine to give amide 21. Ester hydrolysis (for example, using lithium hydroxide in methanol and THF) affords the dicarboxylic acid 22.

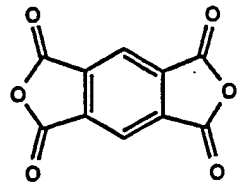
The preparation of a compound having a nucleophilic linking group X to the benzene ring is shown in Scheme VI. The appropriate carboxylic acid R_2CO_2H (where R_2 is as defined previously) is converted to its acid chloride 8 (for example, using oxalyl chloride and a catalytic amount of DMF). The acid chloride can then be reacted with the appropriately substituted benzene 7 to give compound 9.

A preferred process for the preparation of compounds wherein X is NH is shown in Scheme VII. The nitro group of diester 23 (wherein R is loweralkyl) is reduced (for example, using ammonium formate with a palladium on carbon catalyst and the like) to give amine 24. Carbamoyl chloride 25 is prepared from HNR_1R_2 (where R_1 and R_2 are as defined previously herein) and phosgene in an inert solvent such as benzene or toluene. The amine 24 and carbamoyl chloride 25 in the presence of 4-dimethylaminopyridine in pyridine react to give urea 26. Ester hydrolysis (for example, using sodium hydroxide in methanol and THF) affords the desired dicarboxylic acid 27.

A preferred process for the preparation of compounds wherein X is O is also shown in Scheme VII. Hydroxyphthalate 28 (wherein R is loweralkyl) is treated with a base such as sodium hydride in diglyme and then reacted with carbamoyl chloride 25 to give carbamate 29. Ester hydrolysis (for example, using sodium hydroxide in methanol and THF) affords the desired dicarboxylic acid 30.

A preferred process for the preparation of compounds wherein X is CH_2 is shown in Scheme VIII. Diester 31 (wherein R is loweralkyl) is brominated (for example, using N-bromosuccinimide in the presence of 2,2'-azobisisobutyronitrile in carbon tetrachloride) to give the bromomethyl compound 32. Treatment of compound 32 with tris(benzotriazol-1-yl)methane by the method described in Synthesis 666 (1990), which is incorporated herein by reference, affords compound 33 (wherein BT is benzotriazol-1-yl). Compound 33 is converted to carboxy compound 34 by the procedure also described in Synthesis 666 (1990). The carboxy functionality of compound 34 is activated (for example, by treatment with oxalyl chloride to give the acid chloride) and then reacted with HNR_1R_2 (where R_1 and R_2 are as defined previously herein) to give amide 35. Ester hydrolysis (for example, using sodium hydroxide in methanol and THF) affords the desired dicarboxylic acid 36.

SCHEME I



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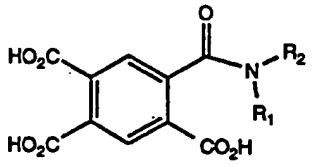

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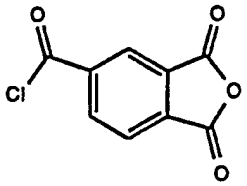

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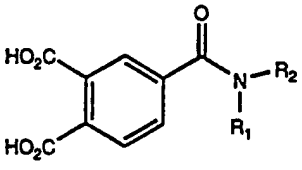

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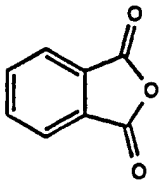

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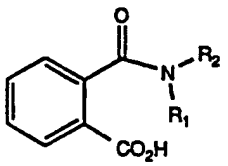

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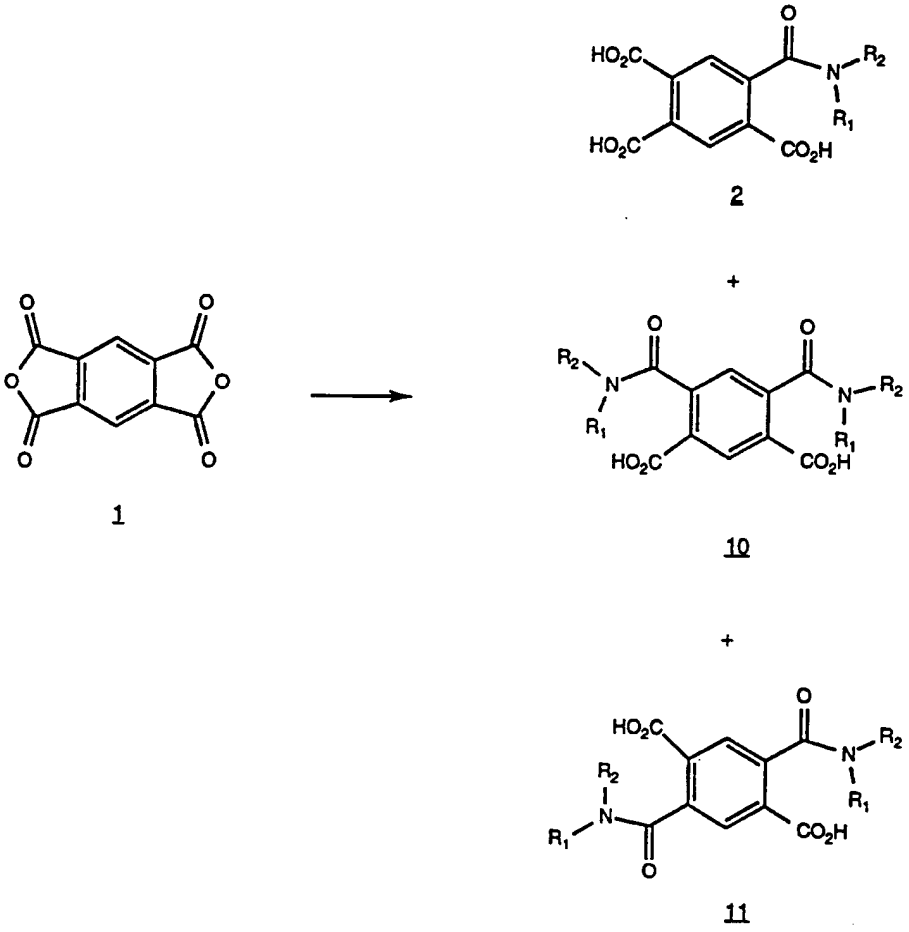
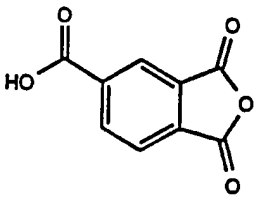
SCHEME II



SCHEME III



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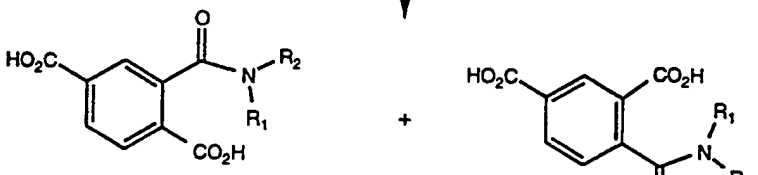
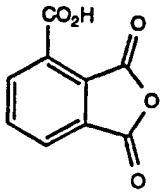


13 + 14

SCHEME IV



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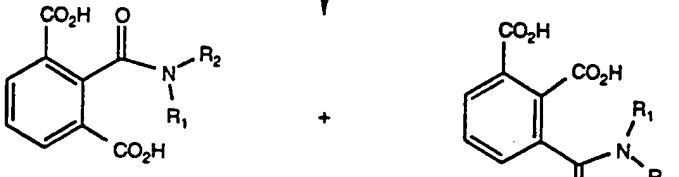
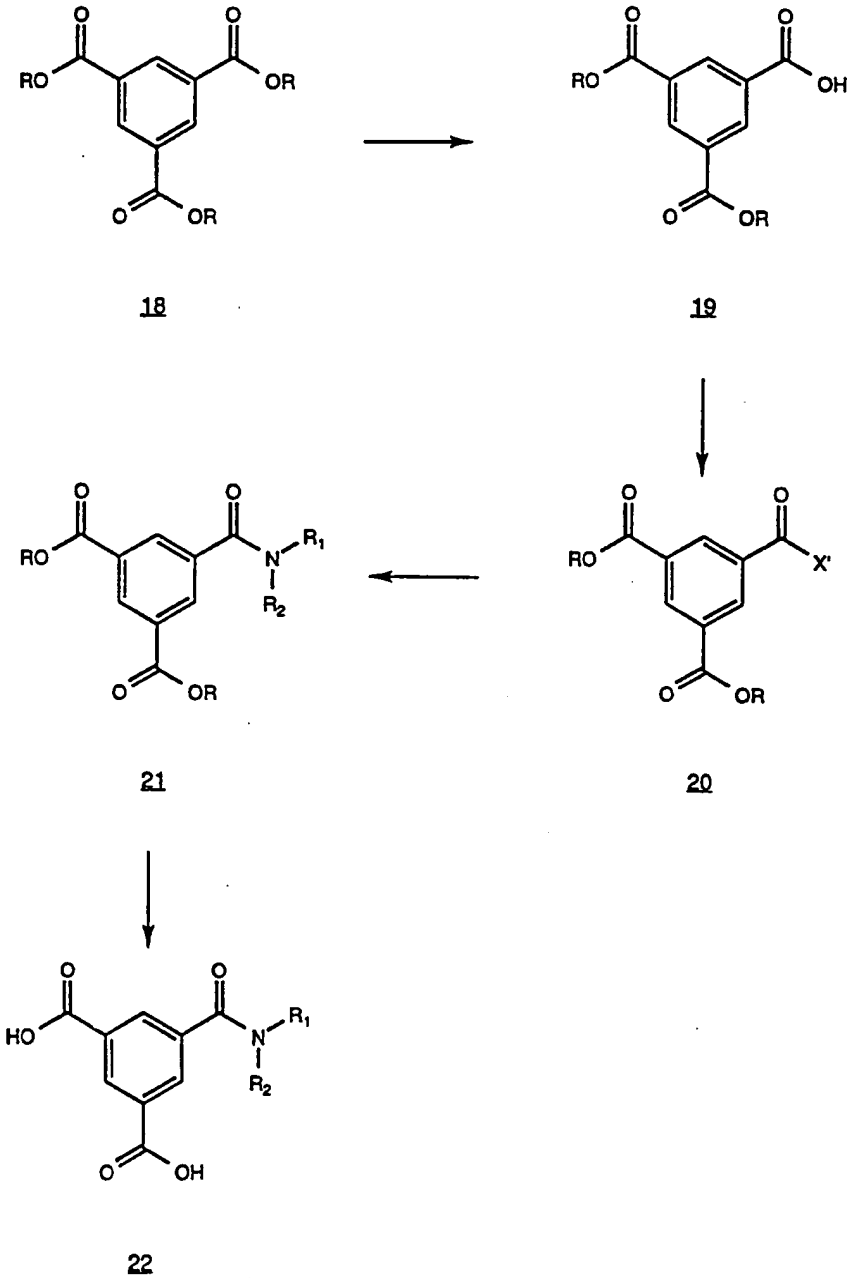
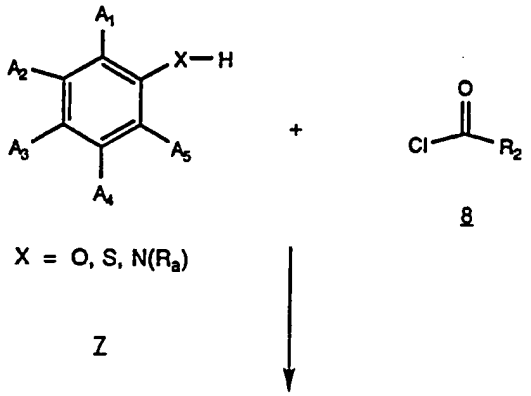


16 + 17

SCHEME V


RO
OR
O
OR
18
RO
OH
O
OR
19
RO
X'
O
OR
20
RO
N
R1
R2
O
OR
21
HO
N
R1
R2
O
OH
22

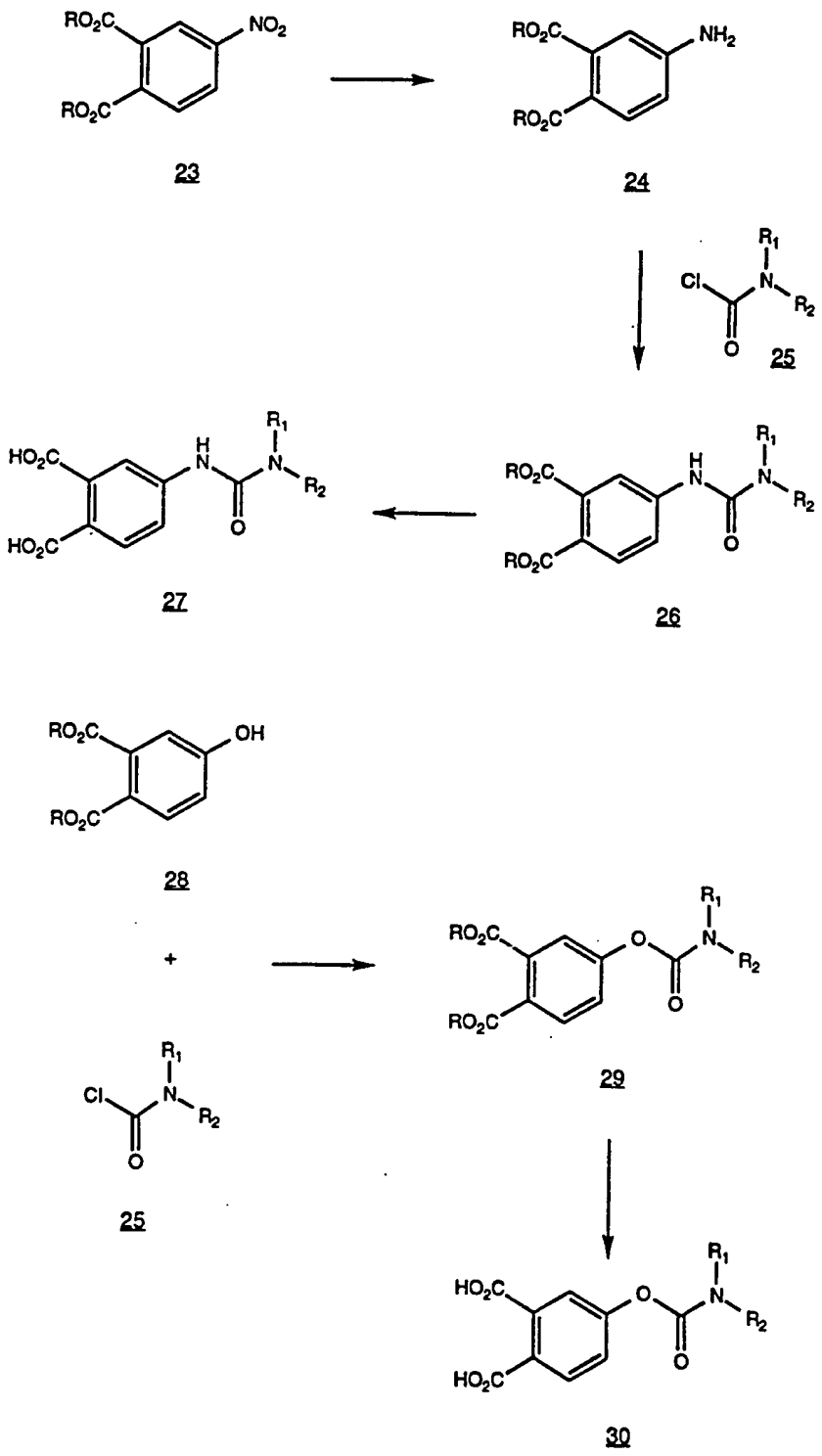
SCHEME VI



8

9

SCHEME VII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RO2C
23
RO2C
NH2
RO2C
24
R1
Cl
N
R2
O
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HO2C
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N
R1
R2
HO2C
O
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RO2C
H
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N
R1
R2
RO2C
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26
RO2C
OH
RO2C
28
+
RO2C
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R1
R2
RO2C
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HO2C
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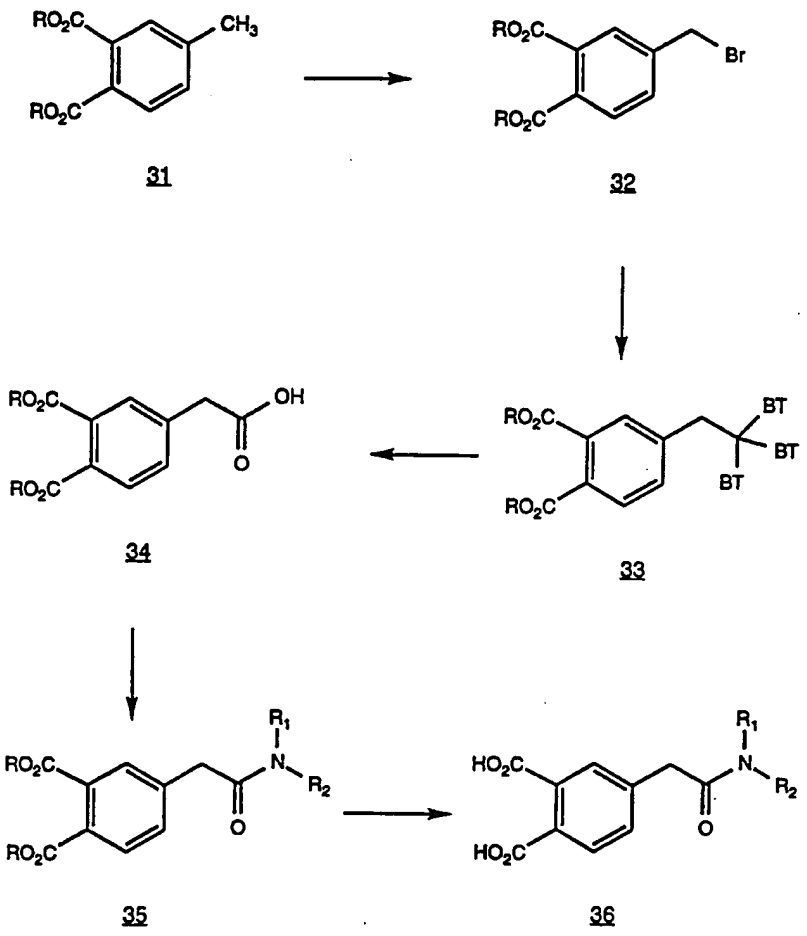
R1
R2
HO2C
O
30

SCHEME VIII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BT
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BT
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O
RO2C
34
RO2C
R1
N
R2
O
RO2C
35
HO2C
R1
N
R2
O
HO2C
36

The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

The following abbreviations were used AgOBn for silver benzoate, BOP-Cl for bis(2-oxo-3-oxazolidinyl)phosphinic chloride, n-BuLi for n-butyl lithium, DIBAL for diisobutylaluminum hydride, DMAP for dimethylaminopyridine, DME for dimethoxyethane, DMF for dimethylformamide, DMSO for dimethylsulfoxide, EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, Et_3N for triethylamine, Et_2O for diethyl ether, EtOAc for ethyl acetate, EtOH for ethanol, HOAc for acetic acid, HOBT for 1-hydroxybenzotriazole, LAH for lithium aluminum hydride, LDA for lithium diisopropylamide, MeOH for methanol, Pd/C for palladium on carbon, THF for tetrahydrofuran, and TPAP for tetrapropylammonium perruthenate.

Example 1

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 1A

N-Benzyl-N-(4-phenoxybenzyl)amine

4-Phenoxybenzaldehyde (5.0 g, 25.2 mmol) and benzylamine (1.46 g, 26.5 mmol) were dissolved in 100 mL of 1% acetic acid in methanol under an atmosphere of dry nitrogen. Sodium cyanoborohydride (1.66 g, 26.5 mmol) was added, and stirring was continued for 18 hours at which time the solvent was removed under reduced pressure. The residue was suspended in ether, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4 to give the title compound.

Example 1B

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

A solution of 1,2,4,5-benzenetetracarboxylic dianhydride (1.2 g, 5.6 mmol), the compound resulting from Example 1A (3.6 g, 12.4 mmol) and Et_3N (1 mL) in toluene (25 mL) was refluxed for 2.5 hours and then left at room temperature overnight. The reaction mixture was then concentrated under reduced pressure. The residue was then taken up in EtOAc, washed with 10% HCl (3x) and a saturated NaCl solution, dried ($MgSO_4$), and evaporated. The residue containing a mixture of isomers was flash silica gel chromatographed eluting with 18:1:1 EtOAc-H_2O-HCO_2H afforded the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 4.20 (d, 4H), 6.80-7.50 (m, 14H), 7.65 (d, 1H), 8.25 (d,1H). MS $(FAB)^+$ m/e 526 $(M+H)^+$. $(FAB)^-$ m/e 524 $(M-H)^-$.

Example 2

2,5-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,4-dicarboxylic acid

Also eluting from the column described in Example 1B was the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 4.20 (d, 8H), 6.80-7.50 (m, 28H), 7.65 (d, 1H), 8.25 (d,1H). MS $(FAB)^+$ m/e 797 $(M+H)^+$. $(FAB)^-$ m/e 795 $(M-H)^-$.

Example 3

4,6-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

Also eluting from the column described in Example 1B was the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 4.20 (d, 8H), 6.80-7.50 (m, 28H), 7.65 (d, 1H), 8.25 (d,1H). MS $(FAB)^+$ m/e 797 $(M+H)^+$. $(FAB)^-$ m/e 795 $(M-H)^-$.

Example 4

Alternate Preparation of

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

To a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.98 g, 4.4 mmol) in 40 mL of acetone and 10 mL acetonitrile cooled in a salt-ice bath was added a solution of the compound resulting from Example 1A (1.3 g, 4.4 mmol) and diisopropylethyl amine (0.57 g , 4.4 mmol) dissolved in 10 mL acetone dropwise over 5 hours *via* syringe pump. After stirring an additional hour, the reaction mixture was evaporated under reduced pressure at room temperature. 6 N HCl (90 mL) and methylene chloride (10 mL) were added to the reaction mixture, which was then stirred at room temperature for 1 hour. The solid which formed was then filtered off. Flash silica gel chromatography eluting with with 95:4:1 $CHCl_3$-MeOH-HOAc yielded 1.81 g (76.5%) of the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 4.20 (d, 4H), 6.80-7.50 (m, 14H), 7.65 (d, 1H), 8.25 (d,1H). MS (FAB)$^+$ m/e 526 $(M+H)^+$. (FAB)$^-$ m/e 524 $(M-H)^-$.

Example 5

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid

A solution of phthalic anhydride (0.41 g, 2.8 mmol), the compound resulting from Example 1A (0.81 g, .8 mmol) and Et_3N (0.5 mL) in toluene (50 mL) was refluxed for 24 hours. The reaction mixture was then concentrated under reduced pressure. The residue was taken up in EtOAc, washed with 5% HCl (3x) and saturated NaCl solution, dried ($MgSO_4$), and evaporated. Flash silica gel chromatography eluting with 95:4:1 CH_2Cl_2-MeOH-HOAc yielded 0.32 g of the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 4.20 (d, 4H), 6.80-8.0 (m, 18H). MS (FAB)$^+$ m/e 438 $(M+H)^+$.

Example 6

2,5-Di[N-phenethyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,4-dicarboxylic acid

The title compound was prepared by the procedures described in Example 1B using N-phenethyl-N-(4-Phenoxybenzyl)amine in place of N-

benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (300 MHz, DMSO-d_6) d 2.70-3.20 (m, 8H), 4.30 (m, 4H), 6.80-7.50 (m, 30H). MS (FAB)$^+$ m/e 825 (M+H)$^+$. (FAB)$^-$ m/e 823 (M-H)$^-$.

Example 7

4,6-Di[N-phenethyl-N-(4-phenoxybenzyl)diaminocarbonyl]benzene-1,3-dicarboxylic acid

The title compound was prepared by the procedures described in Example 1B using N-phenethyl-N-(4-Phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl) amine. ^{1}H NMR (300 MHz, DMSO-d_6) d 2.70-3.20 (m, 8H), 4.30 (m, 4H), 6.80-7.50 (m, 30H). MS (FAB)$^-$ m/e 823 (M-H)$^-$.

Example 8

5-[N-Phenethyl-N-(4-phenoxybenzyl)diaminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4 using N-phenethyl-N-(4-Phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl) amine. ^{1}H NMR (300 MHz, DMSO-d_6) d 2.70-3.20 (m, 4H), 4.30 (m, 2H), 6.80-7.50 (m, 14H). MS (FAB)$^+$ m/e 540 (M+H)$^+$. (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 9

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

To a cold solution of 4-chloroformylphthalic anhydride (1.09 g, 5.2 mmol), prepared by the method described in J. Org. Chem. 38: 2257 (1973), in 40 mL of tetrahydrofuran was added dropwise a solution of Et_3N (0.52 g, 5.2 mmol) and N-benzyl-N-(4-phenoxybenzyl)amine (1.5 g, 5.2 mmol) dissolved in tetrahydrofuran (20 mL). The solution was stirred and allowed to come to room temperature overnight. The reaction was then concentrated *in vacuo* and treated with 6 N HCl (90 mL) and methylene chloride (10 mL) and stirred at room temperature for 1 hour. The mixture was extracted with EtOAc and the combined organic extracts washed with 5% HCl and saturated NaCl solution, dried over magnesium sulfate and concentrated in vacuo. Flash silica gel

chromatography eluting with 95:4:1 CH_2Cl_2-MeOH-HOAc yielded 0.8 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H), 6.80-7.50 (m, 15H), 7.65 (d, 1H), 8.25 (d, 1H). MS (FAB)$^+$ m/e 482 (M+H)$^+$ and (FAB)$^-$ m/e 480 (M-H)$^-$.

Example 10

5-[N,N-Di(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N,N-di(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^1H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H), 6.80-7.50 (m, 18H), 7.65 (s, 1H), 8.25 (s, 1H). MS (FAB)$^+$ m/e 618 (M+H)$^+$ and (FAB)$^-$ m/e 616 (M-H)$^-$.

Example 11

5-[N-(4-Phenoxybenzyl)-N-(4-phenylbutyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N-(4-phenylbutyl-N-(4-phenoxybenzyl)amine in place of the N-benzyl-N-(4-phenoxybenzyl)amine. ^1H NMR (DMSO-d_6, 300 MHz) d 1.20-1.70 (m, 4H), 2.25-3.00 (m, 4H), 4.30 (m, 2H), 6.80-7.50 (m, 14H). MS (FAB)$^+$ m/e 568 (M+H)$^+$ and (FAB)$^-$ m/e 566 (M-H)$^-$.

Example 12

5-(N,N-Dibenzylaminocarbonyl)benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N,N-dibenzylamine in place of the N-benzyl-N-(4-phenoxybenzyl)amine. ^1H NMR (DMSO-d_6, 300 MHz) d 4.20 (s, 4H), 7.10-7.40 (m, 10H), 7.65 (s, 1H), 8.25 (s,1H). MS (FAB)$^+$ m/e 434 (M+H)$^+$ and (FAB)$^-$ m/e 432 (M-H)$^-$.

Example 13

5-[N-(1-Adamantylmethyl)-N-(4-phenoxybenzyl) aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N-(1-adamantyl methyl)-N-(4-phenoxybenzyl)amine in place of the N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) d 0.90-2.00 (m, 3H), 3.20-4.00 (m, 14H), 4.30 (m, 2H), 6.80-7.50 (m, 11H). MS (FAB)$^+$ m/e 584 (M+H)$^+$ and (FAB)$^-$ m/e 582 (M-H)$^-$.

Example 14

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid

To a solution of isophthaloyl dichloride (0.73 g, 3.6 mmol) in 20 mL of tetrahydrofuran was added N-benzyl-N-(4-phenoxybenzyl)amine (1.56 g, 5.4 mmol) and triethylamine (0.52g, 5.4 mmol). The reaction was then refluxed for 2 hours, cooled to room temperature and concentrated *in vacuo*. To the residue was added 10 % HCl, and the reaction mixture was stirred for 10 minutes and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash silica gel chromatography eluting with with 95:4:1 $CHCl_3$-MeOH-HOAc to afford the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H), 6.80-7.50 (m, 14H), 7.60 (m, 1H), 7.70 (d, 1H), 8.00 (m, 2H). MS (FAB)$^+$ m/e 438 (M+H)$^+$ and (FAB)$^-$ m/e 436 (M-H)$^-$.

Example 15

4,5-Dimethoxy-2-[N-(4-Phenoxybenzyl)carbonylamino]benzoic acid methyl ester

To a solution of 4-phenoxyphenylacetic acid (1.14 g, 5 mmol) dissolved in oxalyl chloride (10 mL.) was added a catalytic amoumt of dimethylformamide. The reaction mixture was refluxed for 1 hour and then cooled to room temperature and evaporated. Toluene (2 x 20 mL) was added and evaporated to remove the excess oxalyl chloride. The resulting 4-phenoxyphenylacetyl chloride was then added to a solution of 2-methoxycarbonyl-4,5-dimethoxyaniline (1.0 g, 4.7 mmol) in toluene (20 mL). The reaction was then

stirred at room temperature overnight and evaporated. Water and ethyl acetate were added, the phases were separated, and the organic phase was washed with 5 % NaOH and a saturated solution of NaCl, dried ($MgSO_4$), and evaporated. Flash silica gel chromatography eluting with with 95:4:1 $CHCl_3$-MeOH-HOAc yielded 1.8 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) d 3.75 (s, 3H), 3.80 (d, 7H), 7.00-7.15 (m, 5H), 7.40 (m, 5H), 8.20 (s, 1H). MS $(FAB)^+$ m/e 422 $(M+H)^+$.

Example 16

4,5-Dimethoxy-2-[N-(4-phenoxybenzyl)carbonylamino]benzoic acid

A solution of the compound resulting from Example 15 (0.65 g, 1.3 mmol) and lithium hydroxide monohydrate (0.110 g, 2.6 mmol) in H_2O (10 mL) and tetrahydrofuran (15 mL) was stirred at room temperature for 24 hours. The volatiles were removed under reduced pressure, water was added, and the aqueous solution was washed with ethyl acetate. The aqueous phase was cooled and acidified with 10% HCl and then extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo to afford 600 mg of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) d 3.75 (d, 4H), 3.80 (s, 3H), 7.00-7.15 (m, 5H), 7.40 (m, 5H), 8.20 (s, 1H). MS $(FAB)^+$ m/e 408 $(M+H)^+$.

Example 17

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2,4-triethoxycarbonylbenzene

A solution of the compound resulting from Example 4 (0.30 g, 0.6 mmol), diisopropylamine (0.23 g, 1.8 mmol) and 1.0 M triethyloxonium tetrafluoroborate in dichloromethane (24.0 mL, 2.4 mmol) in 20 mL of methylene chloride was stirred at room temperature for 24 hours. The mixture was washed with 10% HCl (3x), $NaHCO_3$ (3x) and saturated NaCl solution, dried ($MgSO_4$) and evaporated. to give 0.15 g of an amber viscous residue. The oil was purified by flash silica gel chromatography eluting with 5% EtOH in CH_2Cl_2 to give 0.11 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) d 1.25 (m, 9H), 4.28 (m,

6H), 4.65 (d, 4H), 6.80-7.50 (m, 14H), 7.65 (d, 1H), 8.25 (d, 1H). MS (FAB)+ m/e 610 (M+H)+.

Example 18

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4,5-dimethoxybenzoic acid

A solution containing 4,5-dimethoxyphthalic anhydride (1.34 g, 6.4 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (1.85 g, 6.4 mmol), and diisopropylethylamine (0.83 g, 6.4 mmol) in toluene (30 mL) was refluxed for 2 hours. The reaction mixture was then evaporated, and the residue was then taken up in EtOAc, washed with 5% HCl (3x) and saturated sodium chloride solution, dried over magnesium sulfate and evaporated. Flash silica gel chromatography eluting with 95:4:1 CH_2Cl_2-MeOH-HOAc yielded 1.45 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) d 3.60 (d, 3H), 3.80 (d, 3H), 4.20 (m, 4H), 6.80-7.50 (m, 16H). MS (FAB)+ m/e 498 (M+H)+.

Example 19

5-[N-(3,4-Dichlorobenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N-(3,4-dichlorobenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^1H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H) 6.80-7.50 (m, 12H), 7.65 (d, 1H), 8.25 (d,1H). MS (FAB)+ m/e 594 (M+H)+ and (FAB)- m/e 592 (M-H)-.

Example 20

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

and

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,4-dicarboxylic acid

The title compounds were prepared by the procedures described in Example 4, using 1,2,4-benzenetricarboxylic anhydride in place of 1,2,4,5-benzenetetracarboxylic dianhydride. ^1H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H) 6.85-7.50 (m, 14H), 7.60 (d, 1H), 8.10 (m,1H), 8.50 (m,1H). MS (FAB)+ m/e 482 (M+H)+ and (FAB)- m/e 480 (M-H)-

Example 21

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid and

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

The title compounds were prepared by the procedures described in Example 4, using 1,2,3-benzenetricarboxylic anhydride in place of 1,2,4,5-benzenetetracarboxylic dianhydride. ^{1}H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H) 6.80-7.50 (m, 15H), 7.65 (t, 1H), 8.20 (d,1H). MS (FAB)$^+$ m/e 482 (M+H)$^+$ and (FAB)$^-$ m/e 480 (M-H)$^-$

Example 22

5-[N-Benzyl-N-(2-(4-phenoxyphenyl)ethyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 4, using N-benzyl-N-(2-(4-phenoxyphenyl)ethyl)amine in place of 1,2,4,5-benzenetetracarboxylic dianhydride. ^{1}H NMR (DMSO-d_6, 300 MHz) d 4.20 (d, 4H) 6.80-7.50 (m, 12H), 7.65 (d, 1H), 8.25 (d,1H). MS (FAB)$^+$ m/e 540 (M+H)$^+$ and (FAB)$^-$ m/e 539 (M-H)$^-$.

Example 23

5-[N-(3,4-Dichlorobenzyl)-N-(2-(2-naphthoyloxy)ethyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 23A

N-(3,4-Dichlorobenzyl)-N-(2-(2-naphthoyloxy)ethyl)amine

A solution of 3,4-dichlorobenzaldehyde (8.75 g, 0.05 mol), 2-aminoethanol (3.05 g, 0.05 mol), and a catalytic amount of *p*-toluenesulfonic acid in ethanol (100 mL) was refluxed for 6 hours. The reaction was cooled, sodium borohydride (1.89 g, 0.05 mol) was added, and the reaction mixture was stirred at room temperature overnight. Water (50 mL) was added, stirring was continued for an additional 30 minutes, and the mixture was extracted with

EtOAc. The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to give 7.80 g of N-(3,4-dichlorobenzyl)ethanolamine. ^{1}H NMR ($CDCl_3$, 300 MHz) d 3.1 (t, 2H), 3.82 (t, 2H), 4.10 (s, 2H), 7.30 - 8.30 (m, 3H).

To a stirred solution of the ethanolamine prepared above (1.1 g, 5 mmol), 2-naphthoic acid (0.86 g, 5 mmol) and triethylamine (0.5 g, 5 mmol) in CH_2Cl_2 (30 mL) was added EDCI (0.96 g, 5 mmol). The reaction was stirred for 4 hours and then treated with H_2O. The organic layer was separated, washed with 10% NaOH (20 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and evaporated. to give 0.8 g of the title compound as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) d 3.1 (t, 2H), 3.82 (t, 2H), 4.10 (s, 2H), 7.30 - 8.30 (m, 10H). MS (FAB)$^+$ m/e 374 $(M+H)^+$.

Example 23B

5-[N-(3,4-Dichlorobenzyl)-N-(2-(2-naphthoyloxy)ethyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

To a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (1.00 g, 4.5 mmol) in 140 mL of acetone cooled in a salt-ice bath was added a solution of the compound resulting from Example 23A (1.70 g, 4.5 mmol) and diisopropylethylamine (0.84 g , 6.3 mmol) in 10 mL of acetone dropwise over 5 hours *via* syringe pump. After stirring an additional hour the reaction mixture was evaporated under reduced pressure at room temperature. To the residue was added 6 N HCl (90 mL) and methylene chloride (10 mL), and the reaction mixture was stirred at room temperature for 1.5 hours. The solid which formed was then filtered off. Flash silica gel chromatography eluting with with 18:1:1 EtOAc-H_2O-HCO_2H yielded 0.47 g of the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) d 3.80 (m, 2H), 4.20-4.90 (m, 4H), 7.20-8.10 (m, 12H). MS (FAB)$^+$ m/e 610 $(M+H)^+$ and (FAB)$^-$ m/e 608 $(M-H)^-$.

Example 24

4-[N-Benzyl-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

A solution of triethylamine (0.51 g, 5 mmol) and N-benzyl-N-(3-phenoxybenzyl)amine, prepared by the procedure of Example 1A starting from 3-phenoxybenzaldehyde instead of 4-phenoxybenzaldehyde, (1.45 g, 5 mmol) in THF (30 mL) was added dropwise to a stirred solution of 4-chloroformyl-phthalic anhydride, prepared by the procedure described in J. Org. Chem. 38: 2257 (1973), (1.05 g, 5 mmol) in THF (30 mL) at 0 °C. After the addition was complete, the reaction mixture was slowly allowed to warm to ambient temperature overnight. The reaction mixture was concentrated *in vacuo* at 20 °C, and the residue obtained was treated with methylene chloride (10 mL) and 6 N HCl (90 mL) and stirred at ambient temperature for 2 hours. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed successively with 5% HCl, cold water and saturated sodium chloride solution, dried over $MgSO_4$ and concentrated under reduced pressure. The liquid obtained was chromatographed on silica gel eluting with 84.5:13.5:2 $CHCl_3$-MeOH-HOAc to give the product as a mono-methyl ester. The ester was hydrolyzed by refluxing overnight with lithium hydroxide (1.8 g, 43 mmol) in THF (20 mL) and water (12 mL). The reaction mixture was concentrated under reduced pressure to remove the THF, diluted with cold water (20 mL), acidified with dilute HCl, and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with cold water and saturated sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 95:2.5:2.5 EtOAc-HOAc-H_2O to give 1.6 g (65%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 1H), 4.30 (d, 2H), 4.70 (d, 2H), 6.70-7.85 (m, 17H), 9.5 (s, 2H). MS (DCI/NH_3) m/e 481 $(M+H+NH_3-H_2O)^+$, 499 $(M+H+NH_3)^+$.

Example 25

4-[N-Benzyl-N-(4-phenoxymethyl)benzylaminocarbonyl]benzene-1,2-dicarboxylic acid

The title compound was prepared by the procedures described in Example 24 using the analogous N-benzyl-N-(4-phenoxymethyl)benzylamine compound. The crude compound was chromatographed on silica gel eluting with 95:2.5:2.5 EtOAc-HOAc-H_2O to give 1.5 g (61%) of the title compound as a cream colored amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08(d, 1H), 2.25 (q, 1H), 2.35 (s, 1H), 2.50 (t, 1H), 4.00-5.00 (m, 7H), 6.90-7.80 (m, 17H). MS (DCl/NH_3) m/e 496 $(M+H)^+$, 513 $(M+H+NH_3)^+$.

Example 26

5-[(1-(4-Phenoxyphenyl)phenethylaminocarbonyl]benzene-1,3-dicarboxylic acid

A mixture of 4-phenoxyphenyl benzyl ketone (5.5 g, 19 mmol) and benzyl amine (2.04 g, 19 mmol) in methanol (250 mL) was shaken with 5% platinum on carbon (1.1 g) for 16 hours and then for 24 hours under hydrogen at 4 atmospheres. The reaction mixture was filtered and the filtrate evaporated under reduced pressure to give 2-(4-phenoxyphenyl)-1-phenethylamine (7.0 g, 97%) as a colorless solid.

A solution of the above amine (0.54 g, 1.4 mmol) and triethylamine (0.19 mL, 1.4 mmol) in anhydrous methylene chloride was stirred at ambient temperature while a solution of dimethyl 5-chloroformyl-1,3-benzene dicarboxylate (0.33 g, 1.3 mmol), prepared by the procedures described in Photochemistry and Photobiology, 51: 155 (1990), in methylene chloride (15 mL) was added dropwise under a nitrogen atmosphere. After stirring overnight at ambient temperature, the mixture was evaporated under reduced pressure at 20 °C. The solid obtained was chromatographed on silica gel eluting with 8:2 hexane-ethyl acetate to give 442 mg (57%) of 1-[(1-(4-phenoxyphenyl)phenethylaminocarbonyl]-3,5-dimethoxycarbonylbenzene.

The diester (360 mg, 6 mmol) was refluxed overnight in a solution of lithium hydroxide (198 mg, 4.8 mmol) in methanol (9 mL) and water (7 mL). The reaction mixture was cooled, diluted with cold water, acidified with dilute

HCl and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated under reduced pressure to give the title compound as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.40 (d, 2H), 4.75 (d, 1H), 6.78-7.40 (m, 17H), 8.4 (s, 2H). 8.85 (s, 1H). MS (DCI/NH_3) m/e 482 $(M+H)^+$, 499 $(M+H+NH_3)^+$.

Example 27

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1*H*)tetrazolylbenzoic acid

Example 27A

1-Methyl-2-cyanoterephthalate

1-Methyl-2-aminoterephthalate (5.15 g, 26.4 mmol) was slurried in 2 N HCl (50 mL), then sodium nitrite (1.60 g, 23.2 mmol) in water (5 mL) was added. The reaction was mechanically stirred for 1 hour, then the pH was adjusted to 8-9 with solid Na_2CO_3. The resulting solution was then added to a solution of CuCN (2.77 g, 30.9 mmol) and NaCN (3.16 g, 64.5 mmol) in water (30 mL). After stirring at room temperature for 3 hours, the reaction mixture was acidified with concentrated HCl (12 mL), and filtered. The solid was dried under vacuum over P_2O_5 to afford 6.1 g of crude light green solid. The solid was slurried in 9:1 $CHCl_3$-MeOH (140 mL) and filtered. The filtrate was concentrated to give the title compound as a dark yellow solid (3.7 g, 68%) containing ~14% (mole) starting aniline* . ^{1}H NMR (CD_3OD) δ 8.42 (s, 1H), 8.35 (d, 1H), 8.26 (d, 1H), 7.84* (d), 7.40* (d), 7.14* (dd), 4.00 (s, 3H), 3.87* (s). MS (DCI/NH_3) m/e 223 $(M+H+NH_3)^+$.

Example 27B

Methyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-cyanobenzoate

To the compound resulting from Example 27A (320 mg, 1.6 mmol) dissolved in 1:1 CH_2Cl_2-DMF (14 mL) was added N-benzyl-N-(4-phenoxybenzyl)amine (427 mg, 1.48 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (341 mg, 1.78 mmol) and 4-(dimethylamino)pyridine (95 mg, 0.08 mmol). After stirring at room

temperature for 2 days, the reaction was diluted with EtOAc, then washed with 2 x 5% citric acid, 2 x saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by chromatography eluting with 97:3 $CHCl_3$-Et_2O to give 260 mg (40%) of the title compound. ^1H NMR ($CDCl_3$) δ 8.15 (br d, 1H), 7.87 (s, 1H), 7.73 (d, 1H) 7.37 (m, 6H), 7.28 (m, 2H), 7.13 (m, 2H), 7.00 (m, 4H), 4.70 (br d, 2H), 4.33 (br d, 2H), 4.01 (s, 3H). MS (DCI/NH_3) m/e 477 $(M+H)^+$, 494 $(M+H+NH_3)^+$.

Example 27C

Methyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1*H*)tetrazolylbenzoate

To the compound resulting from Example 27B (250 mg, 0.54 mmol) dissolved in DMF (5.4 mL) was added triethylamine hydrochloride (458 mg, 3.33 mmol) and sodium azide (233 mg, 3.58 mmol). The reaction was heated at 110 °C under N_2 for 6 hours, then cooled to room temperature and partitioned between EtOAc and 1 M H_3PO_4. The EtOAc layer was washed with 1 M H_3PO_4, water and brine, dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by chromatography eluting with 1:1 EtOAc-hexane, followed by 98.5:1.5:0.5 $CHCl_3$-MeOH-CH_3CO_2H to afford 182 mg (64%) of the title compound which was lyophilized from CH_3CN-water to give a white solid. ^1H NMR (DMSO-d_6) δ 7.95 (br s,1H), 7.85 (s, 1H), 7.76 (br d, 1H) 7.37 (m, 7H), 7.15 (m, 3H), 6.97 (m, 4H), 4.64 (br d, 2H), 4.44 (br d, 2H), 3.72 (s, 3H). MS (DCI/NH_3) m/e 520 $(M+H)^+$, 537 $(M+H+NH_3)^+$. Anal calcd for $C_{30}H_{25}N_5O_4$: C, 69.35; H, 4.85; N, 13.48. Found: C, 69.06; H, 4.83; N, 12.84.

Example 27D

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1*H*)tetrazolylbenzoic acid

To the compound resulting from Example 27C (100 mg, 0.21 mmol) dissolved in THF (2.8 mL) and MeOH (1 mL) was added 4 N NaOH (0.2 mL). The reaction mixture was stirred at room temperature overnight, then concentrated and partitioned between EtOAc and 1 M H_3PO_4. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a residue that was lyophilized from acetonitrile-water to give the title compound

as a white solid (81 mg). ^{1}H NMR (DMSO-d_6) δ 8.01 (br m, 1H), 7.78 (d, 1H), 7.77 (s, 1H) 7.35 (m, 7H), 7.15 (m, 3H), 6.97 (m, 4H), 4.64 (br d, 2H), 4.42 (br d, 2H). MS (FAB) m/e 506 $(M+H)^+$, 504 $(M-H)^+$. Anal calcd for $C_{29}H_{23}N_5O_4 \cdot 0.5$ H_2O: C, 67.70; H, 4.70; N, 13.61. Found: C, 67.43; H, 4.53; N, 13.29.

Example 28

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1*H*)tetrazolylbenzoic acid

Example 28A

2-Cyano-5-iodobenzoic acid

The title compound was prepared from 2-amino-5-iodobenzoic acid by the method described in J. Org. Chem. 16: 1275 (1951) in 46% yield. ^{1}H NMR (DMSO-d_6) δ 8.40 (s, 1H), 8.18 (d, 1H), 7.76 (d, 1H). MS (FAB) m/e 274 $(M+H)^+$, 291 $(M-H)^+$.

Example 28B

1-Methyl-6-cyanoisophthalate

The compound resulting from Example 28A was treated with trimethylsilyldiazomethane to give the methyl ester. To the ester (155 mg, 0.54 mmol) dissolved in DMF (2 mL) was added water (0.5 mL), followed by anhydrous sodium acetate (172 mg, 2.1 mmol) and palladium(II)acetate (6 mg, 0.026 mmol). The solution was purged with CO, heated under a CO balloon for 3 hours, cooled to room temperature and partitioned between EtOAc and 1 M H_3PO_4. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a solid which was partitioned between Et_2O and saturated $NaHCO_3$. The aqueous layer was acidified and extracted with 3 x Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give 83 mg (75%) of the title compound as a tan solid. ^{1}H NMR (CD_3OD) δ 8.42 (s, 1H), 8.72 (s, 1H), 8.33 (d, 1H), 8.02 (d, 1H),4.01 (s, 3H). MS (DCI/NH_3) m/e 223 $(M+H)^+$, 240 $(M+H+NH_3)^+$.

Example 28C

Methyl 5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-cyanobenzoate

To the compound resulting from Example 28B (80 mg, 0.39 mmol) slurried in CH_2Cl_2 (4 mL) was added oxalyl chloride (57 mg, 0.039 mL, 0.44 mmol) and one drop of DMF. After stirring at room temperature for 45 minutes, the solution was cooled to 0 °C, then treated with a solution of N-benzyl-N-(4-phenoxybenzyl)amine (122 mg, 0.42 mmol) and diisopropylethylamine (118 mg, 0.16 mL, 0.92 mmol) in CH_2Cl_2 (0.5 mL) added dropwise. The cooling bath was removed, and after stirring at room temperature for 3 hours, the same work-up and purification as in Example 27B, except 3:1 hexane-EtOAc was used for the chromatography, to give 50 mg (81%) of the title compound. ^1H NMR ($CDCl_3$) δ 8.22 (s, 1H), 7.82 (d, 1H), 7.73 (d, 1H), 7.35 (m, 7H), 7.13 (m, 2H), 7.00 (m, 5H), 4.72 (br d, 2H), 4.35 (br d, 2H), 3.98 (s, 3H). MS (DCI/NH_3) m/e 477 $(M+H)^+$, 494 $(M+H+NH_3)^+$.

Example 28D

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1*H*)tetrazolylbenzoic acid

Methyl 5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-(1H)tetrazolylbenzoate was prepared from the compound resulting from Example 28C by the method of Example 27C. MS (ESI) m/e 520 $(M+H)^+$.

The title compound was prepared from the ester by the method of Example 27D. ^1H NMR (DMSO-d_6) δ 8.00 (d, 1H), 7.83 (d, 1H), 7.76 (d, 1H) 7.38 (m, 7H), 7.16 (m, 3H), 7.00 (m, 4H), 4.64 (br d, 2H), 4.44 (br d, 2H). MS (DCI/NH_3) m/e 506 $(M+H)^+$, 523 $(M+H+NH_3)^+$. Anal calcd for $C_{29}H_{23}N_5O_4 \cdot 0.65\ H_2O$: C, 67.34; H, 4.74; N, 13.54. Found: C, 67.39; H, 4.77; N, 13.24.

Example 29
4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}benzene-1,2-dicarboxylic acid

Example 29A
Dimethyl 4-aminophthalate

To dimethyl 4-nitrophthalate (1.15 g, 4.80 mmol) dissolved in MeOH (16 mL) was added ammonium formate (2.9 g, 46.0 mmol). The reaction was purged with N_2, then 10 % Pd/C was added. The reaction was heated under reflux for 2.5 hours, cooled to room temperature, filtered through celite and concentrated to give 990 mg (99%) of the title compound as a bright yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H), 6.73 (d, 1H), 6.68 (dd, 1H), 4.18 (br s, 2H), 3.92 (s, 3H), 3.85 (s, 3H). MS (DCI/NH_3) m/e 210 $(M+H)^+$, 227 $(M+H+NH_3)^+$.

Example 29B
Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}phthalate

The compound resulting from Example 29A (247 mg, 1.20 mmol), the compound resulting from Example 122E (496 mg, 1.40 mmol), and 4-dimethylaminopyridine (41 mg, 0.03 mmol) were dissolved in pyridine (2.5 mL) and heated at 100 °C for 4.5 hours. After cooling to room temperature, the reaction mixture was partitioned between 3 N HCl and EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by chromatography eluting with 3:1 hexane-EtOAC to give 115 mg (18%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H), 7.48 (dd, 1H) 7.45-7.25 (envelope, 10H), 7.13 (m, 1H), 7.02 (m, 4H), 6.56 (s, 1H), 4.62 (s, 4H), 3.88 (s, 3H), 3.85 (s, 3H). MS (DCI/NH_3) m/e 542 $(M+H+NH_3)^+$.

Example 29C

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 29B by the method of Example 27D. ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 1H), 7.78 (d, 1H), 7.74 (dd, 1H),7.67 (d, 1H), 7.36 (m, 4H), 7.25 (m, 6H), 7.14 (m, 1H), 6.98 (m, 4H), 4.58 (d, 4H). MS (FAB+) m/e 497 $(M+H)^+$ and (FAB-) m/e 495 $(M-H)^-$. Anal calcd for $C_{29}H_{24}N_2O_6 \cdot 0.25\ H_2O$: C, 69.52; H, 4.93; N, 5.59. Found: C, 69.60; H, 4.89; N, 5.31.

Example 30

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carboxyphenylacetic acid

Example 30A

4-Nitro-2-carboxyphenylacetic acid

Homophthalic acid was nitrated according to the procedure described in J. Org. Chem. 10: 533 (1945) to give the title compound in 52% yield. ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1H), 8.36 (dd, 1H), 7.67 (d, 1H) 4.10 (s, 2H). MS (APCI-) m/e 224 $(M-H)^-$.

Example 30B

Methyl 4-amino-2-carbomethoxyphenylacetate

The compound resulting from Example 30A was treated with trimethylsilyldiazomethane to give the diester which was converted to the aminodiester by the method of Example 29A only refluxing for 1.5 hours. After concentration, the residue was partitioned between EtOAc and water. Isolation of the material in the EtOAc layer gave the title compound. ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 1H), 7.03 (d, 1H), 6.78 (dd, 1H), 3.87 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H). MS (DCI/NH_3) m/e 224 $(M+H)^+$, 241 $(M+H+NH_3)^+$.

Example 30C

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carboxyphenylacetic acid

Methyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carbomethoxyphenylacetate was prepared from the compound resulting from Example 30B by the method of Example 29B. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 1H), 7.48 (dd, 1H) 7.42-7.25 (envelope, 8H), 7.13 (m, 3H), 7.02 (m, 4H), 6.41 (s, 1H), 4.64 (d, 4H), 3.95 (s, 2H), 3.85 (s, 3H), 3.68 (s, 3H). MS (DCI/NH_3) m/e 539 $(M+H)^+$, 556 $(M+H+NH_3)^+$.

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carboxyphenylacetic acid was prepared from the above compound by the method of Example 27D, except the reaction had to be heated under reflux for 4 hours. ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H), 8.05 (d, 1H), 7.68 (dd, 1H), 7.36 (m, 4H), 7.27 (m, 5H), 7.17 (d, 1H), 7.10 (m, 1H), 6.98 (m, 4H), 4.58 (d, 4H), 3.82 (s, 2H). MS (ESI-) m/e 509 $(M-H)^-$. Anal calcd for $C_{30}H_{26}N_2O_6 \cdot 0.65\ H_2O$: C, 68.99; H, 5.27; N, 5.36. Found: C, 68.94; H, 5.08; N, 5.19.

Example 31

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-carboxyphenylacetic acid

Example 31A

Methyl 4-iodo-2-carbomethoxyphenylacetate

To the compound resulting from Example 30B (2.2 g, 10.0 mmol) dissolved in a mixture of 2% HCl (33 mL) and acetone (14 mL) and cooled to -7 °C was added sodium nitrite (745 mg, 10.8 mmol) in water (10 mL) slowly, keeping the reaction temperature <3 °C. The reaction was mechanically stirred for 2 hours, then urea (220 mg, 3.67 mmol) was added, followed by potassium iodide (2.93 g, 17.6 mmol) in water (10 mL). The bath was removed, and the reaction was stirred for 3.5 hours and partitioned between EtOAc and 5% aqueous $NaHSO_3$. The EtOAc layer was washed with 5% aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by chromatography eluting with 8:2 hexane-Et_2O to give

1.15 g (34%) of the title compound, which contained ~15% (mole) of the des-iodo compound*. ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 1H), 8.02* (dd), 7.80 (dd, 1H), 7.49* (ddd), 7.37* (ddd), 7.27* (dd), 7.00 (d, 1H), 4.03* (s), 3.95 (s, 2H), 3.88 (s, >3H due to *), 3.61* (s), 3.60 (s, 3H). MS (DCI/NH_3) m/e 335 $(M+H)^+$, 352 $(M+H+NH_3)^+$.

Example 31B

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-carboxyphenylacetic acid

Methyl 4-carboxy-2-carbomethoxyphenylacetate was prepared from the compound resulting from Example 31A by the method of Example 28B. ^{1}H NMR (CD_3OD) δ 8.60 (d, 1H), 8.14 (dd, 1H), 7.45 (d, 1H), 4.10 (s, 2H), 3.89 (s, 3H), 3.67 (s, 3H). MS (DCI/NH_3) m/e 253 $(M+H)^+$, 270 $(M+H+NH_3)^+$.

Methyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-carbomethoxyphenylacetate was prepared from the above compound by the method of Example 28C. ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H), 7.60 (dd, 1H) 7.42-7.25 (envelope, 8H), 7.13 (m, 3H), 7.00 (m, 4H), 4.70 (br d, 2H), 4.42 (br d, 2H), 4.03 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H). MS (DCI/NH_3) m/e 524 $(M+H)^+$, 541 $(M+H+NH_3)^+$.

The title compound was prepared from the above compound by the method of Example 30C. ^{1}H NMR (DMSO-d_6) δ 7.95 (d, 1H), 7.60 (dd, 1H), 7.30 (m, 8H), 7.15 (m, 3H), 6.98 (m, 4H), 4.55 (br d, 4H), 3.95 (s, 2H). MS (ESI-) m/e 494 $(M-H)^-$. Anal calcd for $C_{30}H_{25}NO_6 \cdot 0.50\ H_2O$: C, 71.42; H, 5.19; N, 2.78. Found: C, 71.46; H, 5.04; N, 2.76.

Example 32

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}benzene-1,2-diacetic acid

Example 32A

Diethyl 4-nitro-1,2-phenylenediacetate

The title compound was prepared from diethyl 1,2-phenylenediacetate by the procedure described in Helv. Chem. Acta, 18: 620 (1935), except the crude product was extracted from the aqueous work-up using Et_2O, and the

residue was purified by chromatography eluting with 8:2 hexane-Et_2O to give the title compound as a light yellow oil in 73% yield. ^1H NMR ($CDCl_3$) δ 8.17 (d, 1H), 8.11 (dd, 1H), 7.45 (d, 1H), 4.16 (m, 4H), 3.80 (s, 4H), 1.25 (m, 6H). MS (DCI/NH_3) m/e 296 $(M+H)^+$, 313 $(M+H+NH_3)^+$.

Example 32B

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}benzene-1,2-diacetic acid

Diethyl 4-amino-1,2-phenylenediacetate was prepared from the compound resulting from Example 32A by the method of Example 30B. ^1H NMR ($CDCl_3$) δ 7.03 (d, 1H), 6.60 (d, 1H), 6.56 (dd, 1H), 4.13 (m, 4H), 3.62 (s, 2H), 3.58 (s, 2H) 1.25 (m, 6H). MS (DCI/NH_3) m/e 266 $(M+H)^+$, 283 $(M+H+NH_3)^+$.

Diethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-1,2-phenylenediacetate was prepared from the above compound by the method of Example 29B. ^1H NMR ($CDCl_3$) δ 7.42-7.25 (envelope, 9H), 7.13 (m, 4H), 7.00 (m, 4H), 6.32 (s, 1H), 4.60 (s, 4H), 4.13 (m, 4H), 3.65 (s, 2H), 3.62 (s, 2H), 1.22 (m, 6H). MS (DCI/NH_3) m/e 598 $(M+H+NH_3)^+$.

The title compound was prepared from the above compound using the method of Example 30C. ^1H NMR (DMSO-d_6) δ 8.59 (s, 1H), 7.36 (m, 6H), 7.25 (m, 5H), 7.10 (m, 2H), 6.98 (m, 4H), 4.55 (br d, 4H), 3.50 (s, 4H). MS (ESI-) m/e 523 $(M-H)^-$. Anal calcd for $C_{31}H_{28}N_2O_6 \cdot 0.35\ H_2O$: C, 70.14; H, 5.45; N, 5.28. Found: C, 70.17; H, 5.33; N, 5.12.

Example 33

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-diacetic acid

Diethyl 4-iodo-1,2-phenylenediacetate was prepared from the compound resulting from Example 32B by the method of Example 31A. The final product contained ~15 mole % of the des-iodo compound*. ^1H NMR ($CDCl_3$) δ 7.52 (s, 1H), 7.46 (d, 1H), 7.27* (s) 7.00 (d, 1H), 4.13 (m, > 4H due to *), 3.71* (s), 3.63 (s, 4H), 1.25 (m, > 6H due to *). MS (DCI/NH_3) m/e 377 $(M+H)^+$, 394 $(M+H+NH_3)^+$.

Diethyl 4-carboxy-1,2-phenylenediacetate was prepared from the above compound by the method of Example 28B. ^{1}H NMR (CD_3OD) δ 7.93 (s, 1H), 7.88 (d, 1H), 7.36 (d, 1H), 4.13 (m, 4H), 3.78 (s, 4H), 1.23 (m, 6H). MS (DCI/NH_3) m/e 295 $(M+H)^+$, 312 $(M+H+NH_3)^+$.

Diethyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2-phenylenediacetate was prepared from the above compound by the method of Example 28C. ^{1}H NMR ($CDCl_3$) δ 7.42-7.20 (envelope, 11H), 7.13 (m, 3H), 7.00 (m, 4H), 4.70 (br d, 2H), 4.43 (br d, 2H), 4.12 (m, 4H), 3.70 (s, 4H), 1.23 (q, 6H). MS (DCI/NH_3) m/e 566 $(M+H)^+$, 583 $(M+H+NH_3)^+$.

The title compound was prepared from the above compound by the method of Example 30C. ^{1}H NMR (DMSO-d_6) δ 7.35 (m, 11H), 7.16 (m, 3H), 6.98 (m, 4H), 4.47 (br d, 4H), 3.64 (s, 2H), 3.62 (s, 2H). MS (ESI-) m/e 508 $(M-H)^-$. Anal calcd for $C_{31}H_{27}NO_6 \cdot 0.25\ H_2O$: C, 72.43; H, 5.39; N, 2.72. Found: C, 72.31; H, 5.25; N, 2.68.

Example 34

5-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carboxyphenylacetic acid

Example 34A

Methyl 2-bromo-4-nitrobenzoate

To 2-bromo-4-nitrotoluene (5.06 g, 23.4 mmol) dissolved in pyridine (23 mL) and water (46 mL) and heated under reflux was added $KMnO_4$ (18.5 g, 117.0 mmol) in portions over 10 minutes. After heating under reflux overnight, the reaction was filtered through celite (while hot), washed well with hot water, and then cooled to room temperature. This solution was washed two times with Et_2O, and the aqueous layer was acidified, saturated with NaCl, and then extracted three times with EtOAc. The combined EtOAc extracts were concentrated in vacuo to afford 3.8 g of crude material. This carboxylic acid was dissolved in MeOH (30 mL), treated with $SOCl_2$ (1 mL), and then heated under reflux overnight. The reaction mixture was cooled and concentrated, and the residue obtained was crystallized from EtOH (25 mL) to give 3.37 g (55%) of

the title compound. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 1H), 8.23 (dd, 1H), 7.93 (d, 1H), 4.00 (s, 3H).

Example 34B

5-Nitro-2-carboxyphenylacetic acid

The compound resulting from Example 34A (1.52 g, 6.2 mmol) was converted to ethyl 2-(2'-carboxy-4'-nitro)phenylacetoacetate by the method described in Tetrahedron, 31: 2607 (1975) to give 1.83 g (100%) crude material as a brown oil. MS (DCI/NH_3) m/e 313 $(M+H+NH_3)^+$.

The above compound (1.83 g, 6.2 mmol) was dissolved in 2 N NaOH (12 mL) and stirred at room temperature for 35 minutes. After acidification with concentrated HCl, the reaction was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, then filtered and concentrated to give 1.5 g of tan solid which was recrystallized from water (25 mL) to give 1.01 g (72%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 8.29 (d, 1H), 8.22 (dd, 1H), 8.10 (d, 1H), 4.11 (s, 2H).

Example 34C

Methyl 5-amino-2-carbomethoxyphenylacetate

The compound resulting from Example 34B was treated with trimethylsilyldiazomethane to give the dimethyl ester, which was converted to the title compound by the method of Example 30B, except the compound was purified by chromatography eluting with 6:4 hexane-EtOAc to give 710 mg (72%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H), 6.58 (dd, 1H), 6.49 (d, 1H), 3.93 (s, 2H), 3.82 (s, 3H), 3.72 (s, 3H). MS (DCI/NH_3) m/e 224 $(M+H)^+$, 241 $(M+H+NH_3)^+$.

Example 34D

Methyl 5-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carbomethoxyphenylacetate

To the compound resulting from Example 34C (150 mg, 0.67 mmol) slurried in toluene (1 mL) was added triphosgene (62 mg, 0.21 mmol) and anhydrous K_2CO_3 (200 mg, 1.45 mmol). The reaction was stirred at 100 °C

under N_2 for 2.5 hours, and then N-benzyl-N-(4-phenoxybenzyl)amine (210 mg, 0.73 mmol) was added. After another 3 hours at 100 °C, the reaction was cooled to room temperature and partitioned between water and EtOAc. The EtOAc layer was washed with 4 x 10% citric acid and brine, dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by chromatography eluting with 3:1 hexane-EtOAc to give 123 mg (36%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H), 7.42-7.20 (envelope, 11H), 7.13 (m, 1H), 7.02 (m, 4H), 6.51 (s, 1H), 4.60 (s, 4H), 3.95 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H). MS (DCI/NH_3) m/e 539 $(M+H)^+$, 556 $(M+H+NH_3)^+$.

Example 34E

5-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-carboxyphenylacetic acid

The title compound was prepared from the compound resulting from Example 34D by the method of Example 30C. ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 7.83 (d, 1H), 7.55 (dd, 1H), 7.45 (d, 1H), 7.35 (m, 4H), 7.26 (m, 5H), 7.12 (m, 1H), 6.98 (m, 4H), 4.59 (d, 4H), 3.84 (s, 2H). MS (FAB+)m/e 511 $(M+H)^+$ and (FAB-) m/e 509 $(M-H)^-$. Anal calcd for $C_{30}H_{26}N_2O_6 \cdot 0.50\ H_2O$: C, 69.35; H, 5.24; N, 5.39. Found: C, 69.40; H, 5.10; N, 5.19.

Example 35

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-carboxyphenylacetic acid

Methyl 5-iodo-2-carbomethoxyphenylacetate was prepared from the compound described in Example 34C by the method of Example 31A. ^{1}H NMR ($CDCl_3$) δ 7.73, 7.72 (both s, total 2H), 7.65 (s, 1H), 3.95 (s, 2H), 3.86 (s, 3H), 3.70 (s, 3H). MS (DCI/NH_3) m/e 335 $(M+H)^+$, 353 $(M+H+NH_3)^+$.

Methyl 5-carboxy-2-carbomethoxyphenylacetate was prepared from the compound described above by the method of Example 28B. ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H), 8.02 (d, 1H), 7.94 (s, 1H), 4.05 (s, 2H), 3.85 (s, 3H), 3.65 (s, 3H). MS (DCI/NH_3) m/e 253 $(M+H)^+$, 270 $(M+H+NH_3)^+$.

Methyl 5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-carbomethoxyphenylacetate was prepared from the compound described

above by the method of Example 28C. ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 1H), 7.45 (d, 1H) 7.37 (m, 9H), 7.13 (m, 2H), 7.00 (m, 4H), 4.70 (br d, 2H), 4.39 (br d, 2H), 4.00 (s, 2H), 3.87 (s, 3H), 3.68 (s, 3H). MS (DCI/NH_3) m/e 524 $(M+H)^+$, 541 $(M+H+NH_3)^+$.

The title compound was prepared from the compound described above by the method of Example 30C. ^{1}H NMR (DMSO-d_6) δ 7.93 (d, 1H), 7.50-7.25 (envelope, 9H), 7.15 (m, 3H), 7.00 (m, 4H), 4.61 (br d, 2H), 4.40 (br d, 1H), 3.97 (s, 2H). MS (FAB+) m/e 496 $(M+H)^+$ and (FAB-) m/e 494 $(M-H)^-$. Anal calcd for $C_{30}H_{25}NO_6 \cdot 0.35\ H_2O$: C, 71.80; H, 5.16; N, 2.79. Found: C, 71.87; H, 5.14; N, 2.55.

Example 36

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]amino}benzene-1,2-dicarboxylic acid

Example 36A

Dimethyl 4-isothiocyanophthalate

To the compound resulting from Example 29A (335 mg, 1.60 mmol) slurried in toluene (1.5 mL) was added thiophosgene (377 mg, 0.25 mL, 3.30 mmol). The reaction mixture was stirred at 75 °C for 5.5 hours, the solution was decanted from insoluble material and concentrated to give 310 mg (77%) of the title compound as a dark brown oil. ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H), 7.52 (d, 1H), 7.35 (dd, 1H), 3.93 (s, 3H), 3.90 (s, 3H). MS (DCI/NH_3) m/e 252 $(M+H)^+$, 269 $(M+H+NH_3)^+$.

Example 36B

Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]amino}phthalate

The compound resulting from Example 36A (290 mg, 1.15 mmol) and N-benzyl-N-(4-phenoxybenzyl)amine (309 mg, 1.07 mmol) were dissolved in toluene (1.2 mL) and heated at 95 °C for 3.5 hours. The reaction was cooled to room tempaerature and partitioned between 10% citric acid and EtOAc. The EtOAc layer was washed with 2 x 10% citric acid and brine, dried over Na_2SO_4, then filtered and concentrated to give a residue which was purified by

chromatography eluting with 3:1 hexane-EtOAc to give 300 mg (52%) of the title compound as light yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H), 7.51 (d, 1H) 7.45-7.25 (envelope, 11H), 7.13 (m, 1H), 7.02 (m, 4H), 5.05 (d, 4H), 3.88 (s, 3H), 3.87 (s, 3H). MS (DCI/NH_3) m/e 541 $(M+H)^+$.

Example 36C

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]amino}benzene-1,2-dicarboxylic acid

The compound resulting from Example 36B was hydrolyzed by the method of Example 27D. The crude product was purified by chromatography using 95:5:1 $CHCl_3$-MeOH-CH_3CO_2H followed by 18:1:1 EtOAC-water-CH_3CO_2H. The resultant glass was partitioned between EtOAc and 2 N HCl, then the EtOAc was washed with 2 N HCl and brine, dried over Na_2SO_4, then filtered and concentrated to give a residue which was dissolved and lyophilized as in Example 27D. ^{1}H NMR (DMSO-d_6) δ 9.58 (s, 1H), 8.10 (d, 1H), 8.03 (s, 1H), 7.57 (d, 1H), 7.30 (m, 9H), 7.14 (m, 1H), 6.98 (m, 4H), 5.05 (d, 4H). MS (FAB-) m/e 511 $(M-H)^-$. Anal calcd for $C_{29}H_{24}N_2O_5S \cdot 0.75\ H_2O$): C, 66.21; H, 4.89; N, 5.32. Found: C, 66.23; H, 4.65; N, 5.04.

Example 37

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methylamino}benzene-1,2-dicarboxylic acid

Example 37A

Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methylamino}phthalate

The compound resulting from Example 29B (100 mg, 0.19 mmol) was added to suspension of 60% NaH (16 mg of dispersion, 9.6 mg NaH, 0.40 mmol) in DMF (1.7 mL). After a few minutes at room temperature, methyl iodide (80 mg, 0.035 mL, 0.57 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between EtOAc and 2 N HCl. The EtOAc was washed with brine, dried over Na_2SO_4, then filtered and concentrated to give a residue which was purified by chromatography eluting

with 95:5 $CHCl_3$-EtOAc to give 81 mg (80%) of the title compound as a tacky solid. ^1H NMR ($CDCl_3$) δ 7.70 (d, 1H), 7.33 (m, 5H), 7.21 (d, 1H), 7.12 (m, 5H), 7.05 (m, 2H), 6.96 (m, 3H), 4.25 (s, 4H), 3.89 (s, 3H), 3.88 (s, 3H), 3.23 (s, 3H). MS (DCI/NH_3) m/e 539 $(M+H)^+$.

Example 37B

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methylamino}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 37A by the method of Example 27D. ^1H NMR (DMSO-d_6) δ 7.66 (d, 1H), 7.36 (m, 5H), 7.17 (m, 7H), 6.97 (m, 4H), 4.23 (d, 4H), 3.11 (s, 3H). MS (FAB+) m/e 511 $(M+H)^+$ and (FAB-) m/e 509 $(M-H)^-$. Anal calcd for $C_{30}H_{26}N_2O_6 \cdot 0.30\ H_2O$: C, 69.84; H, 5.20; N, 5.43. Found: C, 69.81; H, 5.18; N, 5.35.

Example 38

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]oxy}benzene-1,2-dicarboxylic acid

Example 38A

Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]oxy}phthalate

Sodium hydride (61 mg of 60% dispersion, 37 mg NaH, 1.53 mmol) was slurried in diglyme (2 mL), then with mechanical stirring, dimethyl 4-hydroxyphthalate (280 mg, 1.33 mmol) was added. After 20 minutes, the compound resulting from Example 122E (460 mg, 1.30 mmol) was added, and the reaction mixture was stirred reaction at 100 °C for 1.5 hours. The reaction was cooled to room temperature and partitioned between water and EtOAc. Brine was added to the aqueous layer, which was then extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, then filtered and concentrated to give a residue which was purified by chromatography eluting with 4:1 hexane-EtOAc to give 500 mg (73%) of the title compound as a tacky solid. ^1H NMR ($CDCl_3$) δ 7.79 (d, 1H), 7.50 (s, 1H), 7.41-

7.20 (envelope, 10H), 7.12 (m, 1H), 7.00 (m, 4H), 4.55 (m, 4H), 3.91 (s, 3H), 3.90 (s, 3H). MS (DCI/NH_3) m/e 526 $(M+H)^+$, 543 $(M+H+NH_3)^+$.

Example 38B

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]oxy}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 38A by the method of Example 36C. ^1H NMR (DMSO-d_6) δ 7.66 (d, 1H), 7.38 (m, 11H), 7.14 (m, 1H), 7.00 (m, 4H), 4.63 (br d, 2H), 4.52 (br d, 2H). MS (FAB-) m/e 496 $(M-H)^-$. Anal calcd for $C_{29}H_{23}NO_7 \cdot 0.50\ H_2O$: C, 68.77; H, 4.78; N, 2.77. Found: C, 68.90; H, 4.51; N, 2.60.

Example 39

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methyl}-1,2-benzene dicarboxylic acid

Example 39A

Dimethyl 4-bromomethylphthalate

To a solution of dimethyl 4-methylphthalate (3.15 g, 15.1 mmol) dissolved CCl_4 (60 mL) was added N-bromosuccinimide (2.74 g, 15.4 mmol) and 2,2'-azobisisobutyronitrile (122 mg, 0.9 mmol). The reaction was heated under reflux for 1 day, cooled to room temperature, and then chilled at 5 °C for 1.5 hours before filtering through celite. The filtrate was concentrated to 4.4 g of crude oil, which by ^1H NMR ($CDCl_3$) was approximately 65 mole % title compound (s, 4.50 ppm, $ArCH_2Br$), 18 mole % dibromide (s, 6.63 ppm, $ArCHBr_2$), and 17 mole % starting material (s, 2.42 ppm, $ArCH_3$).

Example 39B

Dimethyl 4-{2'-[tris(benzotriazol-1-yl)]ethyl}phthalate

The title compound was prepared from tris(benzotriazol-1-yl)methane (1.1 g, 3.0 mmol) and the compound resulting from Example 39A (1.0 g, which contained ~650 mg, 2.3 mmol bromomethyl compound) by the method described in Synthesis, 666 (1990); this is the reference for the synthesis of

tris(benzotriazol-1-yl)methane as well. The crude material was purified by chromatography eluting with 6:4 hexane-EtOAc to give 500 mg (38%) of the product as a brown glass. ^{1}H NMR ($CDCl_3$) δ 8.09 (m, 3H), 7.41-7.20 (envelope, 8H), 6.95 (m, 4H), 5.44 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H). MS (DCI/NH_3) m/e 591 $(M+H+NH_3)^+$.

Example 39C

Dimethyl 4-carboxymethylphthalate

The title compound was prepared from the compound resulting from Example 39B (492 mg, 0.86 mmol) by the method described in Synthesis, 666 (1990). The crude material was purified by chromatography eluting with 6:4 hexane-EtOAc followed by 98.5:1.5:0.5 $CHCl_3$-MeOH-CH_3CO_2H to give 105 mg (48%) of the title compound as a brown solid. ^{1}H NMR (CD_3OD) δ 7.70 (d, 1H), 7.63 (d, 1H), 7.52 (dd, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.70 (s, 2H). MS (DCI/NH_3) m/e 253 $(M+H)^+$, 270 $(M+H+NH_3)^+$.

Example 39D

Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methyl}phthalate

The title compound was prepared from the compound resulting from Example 39C by the method of Example 28C. ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 1H), 7.56 (m, 1H), 7.47-7.28 (envelope, 6H), 7.23-6.92 (envelope, 9H), 4.63 (d, 2H), 4.43 (d, 2H), 3.90, 3.88 (both s, total 6H), 3.83 (d, 2H). MS (DCI/NH_3) m/e 524 $(M+H)^+$, 541 $(M+H+NH_3)^+$.

Example 39E

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]methyl}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 39D by the method of Example 27D. ^{1}H NMR (DMSO-d_6) δ 7.61 (m, 1H), 7.53 (m, 1H), 7.45-7.10 (envelope, 11H), 6.97 (m, 4H), 4.61 (d, 2H), 4.50 (d, 2H), 3.93 (d, 2H). MS (FAB+) m/e 496 $(M+H)^+$ and (FAB-) m/e 494 $(M-H)^-$. Anal calcd for $C_{30}H_{25}NO_6 \cdot 0.50\ H_2O$: C, 71.42; H, 5.19; N, 2.78. Found: C, 71.30; H, 5.06; N, 2.62.

Example 40
4-[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]benzene-1,2-dicarboxylic acid

Example 40A
Dimethyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]phthalate

To the compound resulting from the first two sentences of Example 9 (200 mg, 0.40 mmol) dissolved in THF (0.8 mL) was added Lawesson's reagent (225 mg, 0.56 mmol). The reaction was stirred at room temperature for 4 days and then concentrated to give a residue which was purified by chromatography eluting with 85:15 hexane-EtOAc to give 100 mg (48%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.49 (m, 1H) 7.37 (m, 7H), 7.13 (m, 1H), 7.02 (m, 6H), 5.39 (v br s, 2H), 4.55 (d, 2H), 3.90, 3.89, 3.88 (all s, total 6H). MS (DCI/NH_3) m/e 526 $(M+H)^+$, 543 $(M+H+NH_3)^+$.

Example 40B
4-[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 40A by the method of Example 27D. ^{1}H NMR (DMSO-d_6) δ 7.72 (m, 1H), 7.60 (m, 1H), 7.57-7.30 (envelope, 8H), 7.20-6.90 (envelope, 7H), 5.41 (d, 2H), 4.63 (d, 2H). MS (FAB+) m/e 498 $(M+H)^+$ and (FAB-) m/e 496 $(M-H)^-$. Anal calcd for $C_{29}H_{23}NO_5S \cdot 1.20\ H_2O$: C, 67.09; H, 4.93; N, 2.70. Found: C, 67.03; H, 4.63; N, 2.90.

Example 41
5-[N-Benzyl-N-(2-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

.N-Benzyl-N-(2-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the 4-phenoxybenzaldehyde with 2-phenoxybenzaldehyde.

The title compound was prepared by the procedures described in Example 4 using N-benzyl-N-(2-phenoxybenzyl) amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.15 (d, 4H), 6.60-7.50 (m, 14H), 7.60 (d,1H) , 8.25 (d,1H). MS (FAB)$^+$ m/e 526 (M+H)$^+$ and (FAB)$^-$ m/e 524 (M-H)$^-$.

Example 42

5-[N-Benzyl-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-(3-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the 4-phenoxybenzaldehyde with 3-phenoxybenzaldehyde.

The title compound was prepared by the procedures described in Example 4 using N-benzyl-N-(3-phenoxybenzyl) amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (d, 4H), 6.75-7.40 (m, 14H), 7.60 (d, 1H), 8.15 (d,1H). MS (FAB)$^+$ m/e 526 (M+H)$^+$ and (FAB)$^-$ m/e 524 (M-H)$^-$.

Example 43

5-[N-Benzyl-N-(4-phenylbenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-(4-phenylbenzyl)amine was prepared using the same procedure of Example 1A replacing the 4-phenoxybenzaldehyde with 4-phenylbenzaldehyde.

The title compound was prepared by the procedures described in Example 4 using N-benzyl-N-(4-phenylbenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (s, 4H), 7.20 -7.78 (m, 15H), 8.25 (s, 1H). MS (FAB)$^+$ m/e 510 (M+H)$^+$ and (FAB)$^-$ m/e 508 (M-H)$^-$.

Example 44

5-[N-Cyclohexylmethyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-Cyclohexylmethyl-N-(4-phenoxybenzyl)amine was prepared using the same procedure of Example 1A replacing the benzylamine with cyclohexylmethylamine.

The title compound was prepared by the procedures described in Example 4 using N-cyclohexyl-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.80 -1.80 (m, 8H), 2.40-2.80 (m, 2H), 4.00 (m, 2H), 4.3 (s,2H), 6.90 -7.60 (m, 10H), 8.25 (d, 1H). MS (FAB)$^+$ m/e 610 (M+H)$^+$ and (FAB)$^-$ m/e 608 (M-H)$^-$.

Example 45

5-[N-(3,4-Difluorobenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(3,4-Difluorobenzyl)-N-(4-phenoxybenzyl)amine was prepared using the same procedure of Example 1A replacing the benzylamine with 3,4-difluorbenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3,4 difluorobenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (s, 2H), 4.6 (m, 2H), 6.80-7.25 (m, 12H), 7.65 (d, 1H), 8.25 (d,1H). MS (FAB)$^+$ m/e 562 (M+H)$^+$ and (FAB)$^-$ m/e 560 (M-H)$^-$.

Example 46

5-[N-(3-Triluoromethylbenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(3-Trifluoromethylbenzyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 3-trifluormethylbenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3- trifluoromethylbenzyl)-N-(4-phenoxybenzyl)amine in

place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.25 (s, 2H), 4.40 (s, 2H), 6.80 -7.80 (m, 14H), 8.30 (d, 1H). MS (FAB)$^+$ m/e 594 (M+H)$^+$ and (FAB)$^-$ m/e 592 (M-H)$^-$.

Example 47

5-[N-(2-Trifluoromethylbenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Trifluoromethylbenzyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 2-trifluormethylbenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- trifluoromethylbenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.25 (s, 2H), 4.40 (s, 2H), 6.80 -7.95 (m, 13H),8.15 (s,1H), 8.80 (d, 1H). MS (FAB)$^+$ m/e 594 (M+H)$^+$ and (FAB)$^-$ m/e 592 (M-H)$^-$.

Example 48

5-[N-(2-Methoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Methoxybenzyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 2-methoxybenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- methoxylbenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.60 (s, 3H), 4.20 (d, 2H), 4.60 (s, 2H), 6.80 - 7.25 (m, 13H), 7.90 (s, 1H), 8.45 (s, 1H). MS (FAB)$^+$ m/e 556 (M+H)$^+$ and (FAB)$^-$ m/e 554 (M-H)$^-$.

Example 49

5-[N-(2-Methylbenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Methylbenzyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 2-methylbenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- methyllbenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.95 (s , 3H), 4.20 (d, 2H), 4.75 (s, 2H), 6.80 -7.50 (m, 13H), 7.50 (d, 1H), 8.15, (d, 1H). MS (FAB)$^+$ m/e 610 (M+H)$^+$ and (FAB)$^-$ m/e 608 (M-H)$^-$.

Example 50

5-[N-(4-Nitrobenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(4-Nitrobenzyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 4-nitrobenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(4-nitrobenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.25 (d, 2H), 4.70 (m, 2H), 6.80 -7.80 (m, 12H), 8.00-8.20 (m, 3H). MS (FAB)$^+$ m/e 571 (M+H)$^+$ and (FAB)$^-$ m/e 569 (M-H)$^-$.

Example 51

5-[N-(Naphth-1-ylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(Naphth-1-ylmethyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with naphth-1-ylmethylamine.

The title compound was prepared by the procedures described in Example 4 using N-(Napth-1-ylmethyl)-N-(4-phenoxybenzyl)amine in place of

N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (s, 1H), 4.60 (s, 1H), 5.10 (s, 2H), 6.65 -8.20 (m, 18H). MS (FAB)$^+$ m/e 576 (M+H)$^+$ and (FAB)$^-$ m/e 574 (M-H)$^-$.

Example 52

5-[N-(3-Phenylpropyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(3-Phenylpropyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 3-phenylpropylamine.

The title compound was prepared by the procedures described in Example 4 using N-(3-phenylpropyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.60-1.90 (m, 2H), 2.80 (m, 2H), 4..25 (s, 2H), 4.75 (m, 2H) 6.90 -7.45 (m, 14H), 7.60 (d, 1H), 8.25 (d, 1H). MS (FAB)$^+$ m/e 554 (M+H)$^+$ and (FAB)$^-$ m/e 552 (M-H)$^-$.

Example 53

5-[N-(2-Thienylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Thienylmethyl)-N-(4-phenoxybenzyl) amine was prepared using the same procedure of Example 1A replacing the benzylamine with 2-thienylmethylamine.

The title compound was prepared by the procedures described in Example 4 using N-(2-thienylmethyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (s, 2H), 4.80 (s, 2H), 6.80 -7.25 (m, 12H), 8.00 (m, 1H), 8.60 (m, 1H). MS (FAB)$^+$ m/e 532 (M+H)$^+$ and (FAB)$^-$ m/e 530 (M-H)$^-$.

Example 54

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4-methoxycarbonyl-benzene-1,2-dicarboxylic acid

To a solution of the compound resulting from Example 72A (0.25 g, 0.9 mmol) and Et_3N (0.125 mL, 0.9 mmol) in 15 mL of THF and cooled to 0 °C was added a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.25 g, 0.9 mmol) in 5 mL THF slowly over 5 minutes. The reaction mixture was stirred for 1 hour at 0 °C before adding a solution of MeOH (0.034 mL, 0.9 mmol), Et_3N (0.125 mL, 0.9 mmol) contained in 5 mL of THF. The reaction was then stirred for another hour at 0 °C before evaporation. To the residue was added 5 mL of CH_2Cl_2, 5 mL of THF, and 15 mL of 10% HCl, and the mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure, H_2O was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl and evaporated. (0.4 g). Flash silica gel chromatography eluting with 95:4:1 $CHCl_3$-MeOH-HOAc yielded the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.80 (m, 3H), 4.20 (d, 2H), 4.80 (m, 2H), 6.80 - 7.45 (m, 14H), 7.60 (s,1H), 8.00 (s, 1H). MS $(FAB)^+$ m/e 540 $(M+H)^+$ and $(FAB)^-$ m/e 538 $(M-H)^-$.

Example 55

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2-dimethoxycarbonyl-benzene-4-carboxylic acid

To a solution containing the compound resulting from Example 72A (0.34 g, 1.3 mmol) in 15 mL of THF cooled to -30 °C was added a solution of Et_3N (0.36 mL, 2.6 mmol) and MeOH (0.104 mL, 2.6 mmol) in THF (15 mL) over 5 minutes. The reaction mixture was stirred at -30 °C for 45 minutes, and then a solution of N-benzyl-N-(4-phenoxybenzyl) amine (0.38 g, 1.3 mmol) and Et_3N (0.18 mL, 2.6 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature ovemight and then evaporated and taken up in EtOAc. The reaction mixture was washed with 5% HCl followed by saturated NaCl solution and evaporated to give 0.5 g of crude product. Flash silica gel chromatography eluting with 95:4:1 $CHCl_3$-MeOH-HOAc yielded the title compound. ^1H NMR

(DMSO-d_6, 300 MHz) δ 3.65 (s, 3H), 3.75 (s, 3H), 4.20 (m, 2H), 4.60 (s, 2H), 6.80 -7.60 (m, 12H), 7.90 s,1H), 8.50 (s,1H). MS (FAB)- m/e 552 $(M-H)^-$.

Example 56

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2-methoxycarbonyl-benzene-1,4-dicarboxylic acid

To a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.5 g, 2.3 mmol) in 20 mL of acetone cooled in a salt-ice bath was added a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.66 g, 2.3 mmol) and diisopropylethyl amine (0.3 g , 2.3 mmol) in 10 mL of acetone dropwise over 2 hours *via* syringe pump. After stirring an additional hour, the reaction mixture was evaporated under reduced pressure at room temperature. Methanol was added, and then the reaction mixture was refluxed overnight. The volatiles were removed under reduced pressure, and then 5% HCl was added and the mixture extracted with EtOAc. The combined organic extracts were washed with saturated NaCl solution, and then evaporated to give a foam. Flash silica gel chromatography eluting with 95:4:1 $CHCl_3$-MeOH-HOAc yielded of 0.042 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.80 (d, 3H), 4.20 (m, 2H), 4.6 (m,2H), 6.80 -8.10 (m, 16H). MS $(FAB)^+$ m/e 540 $(M+H)^+$ and $(FAB)^-$ m/e 538 $(M-H)^-$.

Example 57

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1-methoxycarbonyl-benzene-2,4-dicarboxylic acid

The title compound is isolated from the column chromatography described in Example 56 as another fraction.

Example 58

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,4-dimethoxycarbonyl-benzene-2-carboxylic acid

A solution of 1,4-dimethylcarboxylate benzene-2,5-dicarbonyl chloride, prepared according to Kogyo Kagaku Zaashi, 71: 1559, (1968), (0.125 g, 0.4 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (0.06 g, 0.4 mmol), NaOH (0.4 mL, 1 N) and CH_2Cl_2 (20 mL) was stirred at room temperature for 2.5 hours. The volatiles were removed under reduced pressure and then water was added. The aqueous solution was washed with ether and then acidified and extracted with EtOAc. The combined organic extracts were evaporated and the residue obtained (0.092 g) flash silica gel chromatographed eluting with 95:4:1 $CHCl_3$-MeOH-HOAc to yield the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (dd, 6H), 4.20 (d, 2H), 4.75 (m, 2H), 6.90 -7.40 (m, 14H), 7.6 (d,1H), 8.60 (d, 1H). MS $(FAB)^+$ m/e 554 $(M+H)^+$ and $(FAB)^-$ m/e 552 $(M-H)^-$.

Example 59

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-2,4-dimethoxycarbonyl-benzene-1-carboxylic acid

The title compound is prepared by the procedures described in Example 58 except using 1,5-dimethylcarboxylate benzene-2,4-dicarbonyl chloride, prepared according to Kogyo Kagaku Zaashi, 71: 1559, (1968), instead of 1,4-dimethylcarboxylate benzene-2,5-dicarbonyl chloride.

Example 60

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2,4-trimethoxycarbonbenzene

A solution of 5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,2,4-tricarboxylic acid (0.025 g, 0.074 mmol), MeOH (8 µL, 2 mmol), acetone (2 mL), and CH_2Cl_2 (1 mL) was cooled to 0 °C. To this solution was added $Me_3SiCH_2N_2$(2 M in hexane, 0.095 mL) over 5 minutes. The reaction was then stirred for 30 minutes and evaporated to afford the title compound as an amorphous solid (20 mg). MS $(FAB)^+$ m/e 568 $(M+H)^+$.

Example 61

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2-benzenedicarboxylic dianhydride-4-carboxylic acid sodium salt

To a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.5 g, 2.3 mmol) in 20 mL of acetone cooled in a salt-ice bath was added a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.66 g, 2.3 mmol) and diisopropylethylamine (0.3 g , 2.3 mmol) in 10 mL of acetone dropwise over 2 hours *via* syringe pump. After stirring an additional hour, the reaction mixture was evaporated under reduced pressure at room temperature, treated with 5% HCl and extracted with EtOAc. The combined organic extracts were washed with saturated NaCl solution and then evaporated to give a foam. This was then taken up in cold methanol (2 mL) and treated with a solution of NaOH (1 molar equivalent), stirred for 5 minutes and evaporated to afford a solid. ^1H NMR (D_2O, 300 MHz) δ 3.80 (m, 2H), 4.20 - 4.90 (m, 4H), 7.20 -8.10 (m, 14H). MS m/e 552 $(M+Na)^+$.

Example 62

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,2-dimethoxycarbonylbenzene

To a solution of 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,2-dicarboxylic acid (0.1 g, 0.2 mmol), MeOH (0.015 mL, 0.4 mmol), acetone (5 mL) and CH_2Cl_2 (1 mL) cooled to 0 °C was added $Me_3SiCH_2N_2$ (2 M in hexane) (0.2 mL) over 5 minutes. The reaction was then stirred for 30 minutes and evaporated to give 4.8 mg of the title compound as an amorphous solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.80 (dd, 6H), 4.40 (m, 2H), 4.60 (m, 2H), 6.90 -8.20 (m, 17H). MS $(FAB)^+$ m/e 510 $(M+H)^+$.

Example 63

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzoic acid

To a solution of homophthalic anhydride (0.81 g, 5 mmol), diisopropylethyl amine (0.87 mL, 5 mmol) and THF (20 mL) cooled to 0 °C was added a solution of N-benzyl-N-(4-phenoxybenzyl)amine (1.44 g, 5 mmol) in 10 mL THF slowly over 2 hours. The reaction was allowed to come to room

temperature overnight and then evaporated. To the residue was added 10% HCl, and the solution was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated. The oil was then crystallized from hot CH_3CN to give the title compound as a white solid (0.51 g). ^1H NMR (DMSO-d_6, 300 MHz) δ 4.20 (d, 2H), 4.45 (d, 2H) 4.60 (d, 2H), 6.90 -7.50 (m, 16H) 7.95 (dd, 2H). MS $(FAB)^+$ m/e 452 $(M+H)^+$.

Example 64

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4-methoxybenzene-1-sulfonamide

A solution of 4-methoxy-1-aminosulfonylbenzene-3-carboxylic acid (0.232 g, 1 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (0.289 g, 1 mmol), N-hydroxybenzotriazole-H_2O (0.135 g, 1 mmol), and dicyclohexyl-carbodiimide (0.191 g, 1 mmol) in 20 mL THF was stirred at room temperature for 72 hours. The volatiles were removed under reduced pressure, water was added to the residue, and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with 10 % HCl, dried ($MgSO_4$) and evaporated. The crude product was crystalized from acetonitrile and then further purified by flash column chromatography on silica gel eluting with 95:4:1 $CHCl_3$-MeOH-HOAc to afford 0.067 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.90 (d, 2H), 4.20 - 4.50 (m, 3H), 4.80 (m, 1H), 6.90 -7.40 (m, 15H), 7.80 (m, 2H). MS $(FAB)^+$ m/e 503 $(M+H)^+$.

Example 65

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzoic acid

To a solution of terephthaloyl chloride (1.06 g, 5.2 mmol) and Et_3N (0.75 g, 7.8 mmol) in 20 mL of THF cooled to 0 °C was added N-benzyl-N-(4-phenoxybenzyl)amine (2.25 g, 7.8 mmol) in 10 mL THF slowly over 15 minutes. The reaction was then stirred overnight. The volatiles were removed under reduced pressure, 10% NaOH solution was added and the solution was washed with ethyl ether. The aqueous phase was then acidified with 10 % HCl and extracted with EtOAc. The combined organic extracts were washed with saturated NaCl solution, dried and evaporated. The crude product was purified

by flash silica gel chromatography eluting with 95:4:1 $CHCl_3$-MeOH-HOAc to give 0.039 g of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.40 (d, 2H), 4.60 (d, 2H), 6.90 -7.50 (m, 14H), 7.60 (d, 2H), 8.00 (d, 2H). MS $(FAB)^+$ m/e 438 $(M+H)^+$.

Example 66

1-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]biphenyl-1'-carboxylic acid

A solution of diphenic anhydride (1.12 g. 5 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (1.44 g, 0.005 mol) and triethylamine (0.5 g, 5 mmol) in 50 mL of toluene was refluxed for 2 hours and then left at room temperature overnight. The toluene was evaporated, ethyl acetate was added to the residue and the resulting solution was washed with saturated NaCl solution, dried and evaporated. Recrystallization of the oil from hot acetonitrile yielded 0.665 g of the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.60 (m, 2H), 4.60 - 5.10 (m, 2H), 6.50 -7.60 (m, 20H), 7.9 (m, 2H). MS $(FAB)^+$ m/e 514 $(M+H)^+$ and $(FAB)^-$ m/e 512 $(M-H)^-$.

Example 67

5-[N-Benzyl-N-(L-methionine ethyl ester)aminocarbonylmethyl]benzene-1,2,4-tricarboxylic acid

N-Benzyl-L-methionine ethyl ester was prepared using the same procedure as given for the preparation for N-benzyl-N-(4-phenoxybenzyl)amine except replacing the 4-phenoxybenzylamine with L-methionine ethyl ester.

The title compound was prepared by the procedures described in Example 4 using N-benzyl-N-(L-methionine ethyl ester)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.30 (dt, 3H), 1.60 -2.60 (m, 8H), 3.20 (m, 2H), 4.20-4.40 (m, 2H), 7.20 -8.40 (m, 7H). MS $(FAB)^+$ m/e 504 $(M+H)^+$ and $(FAB)^-$ m/e 502 $(M-H)^-$.

Example 68

5-[N-Benzyl-N-(L-methionine methyl ester)aminocarbonylmethyl]benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-(L-methionine methyl ester) amine was prepared using the same procedure as given for the preparation for N-Benzyl-N-(4-phenoxybenzyl) amine except replacing the 4-phenoxybenzyl amine with L-methionine methyl ester amine.

The title compound was prepared by the procedures described in Example 4 substituting N-benzyl-N-(L-methionine methyl ester)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.20 (dt, 3H), 1.60 - 2.60 (m, 8H), 3.20 (m, 2H), 4.20 - 4.40 (m, 2H), 7.20 - 8.40 (m, 7H). MS (FAB)$^+$ m/e 490 (M+H)$^+$ and (FAB)$^-$ m/e 488 (M-H)$^-$.

Example 69

5-[N-Benzyl-N-(L-methionine)aminocarbonylmethyl]benzene-1,2,4-tricarboxylic acid

To a solution of 5-[N-benzyl-N-(L-methionine methyl ester)aminocarbonyl]benzene-1,2,4-tricarboxylic acid (0.160 g, 0.3 mmol) in THF (9 mL) and water (1 mL) was added lithium hydroxide monohydrate (0.130 g, 3.3 mmol). The reaction was then heated for 2 hours and then evaporated to remove volatiles. The solution was acidified and then extracted with ethyl acetate. The combined organic extracts were washed with saturated NaCl solution and evaporated to yield a solid (0.075 g). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.40 - 2.60 (m, 8H), 3.60 (m, 2H), 4.10 - 4.20 (m, 2H), 7.20 - 8.20 (m, 7H). MS (FAB)$^+$ m/e 476 (M+H)$^+$ and (FAB)$^-$ m/e 474 (M-H)$^-$.

Example 70

5-[N-Benzyl-N-(*syn*-(4-acetoxy-5-methyl-6-phenylhexyl)aminocarbonylmethyl]benzene-1,2,4-tricarboxylic acid

Example 70A

syn -(1-Methyl-2-hydroxy)-5-benzyloxypentylphenyl ketone

$TiCl_4$ (1.0 M solution in CH_2Cl_2, 16.8 mL) was added dropwise to a -78 °C solution of propiophenone (2.05 g, 15.2 mmol) in 77 mL CH_2Cl_2. After 5 minutes at -78 °C, Et_3N (2.3 mL, 16.8 mmol) was added, and the reaction mixture was stirred at -78 °C for 0.5 hours. 4-Benzyloxybutyraldehyde (3.0 g, 16.8 mmol), prepared by the method described in Heterocycles 28(2): 663, (1989), was added dropwise, neat. The reaction mixture was stirred for 0.5 hours at -78 °C and then was quenched by the addition of 50% saturated NH_4Cl solution. The solution was warmed to room temperature and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed on silica gel eluting with 85:15 hexane-ethyl acetate to afford the title compound (3.67 g) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, 3H), 1.60 (t,3H), 1.67-1.88 (m, 2H), 3.52 (m, 3H), 4.03 (m, 1H), 4.51 (s, 2H), 7.32 (s, 5H), 7.48 (t, 2H), 7.59 (t, 2H), 7.95 (d, 2H). MS (DCI/NH_3) m/e 313 $(M+H)^+$.

Example 70B

syn -(1-Methyl-2-acetoxy)-5-benzyloxypentylphenyl ketone

Acetic anhydride (1.1 mL, 11.7 mmol) was added dropwise to a 0 °C solution of the compound resulting from Example 70A and a catalytic amount of DMAP in 100 mL CH_2Cl_2. The reaction mixture was stirred for 24 hours at room temperature, then 0.1 N HCl was added. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated to afford the title compound (2.9 g) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H), 1.58-1.75 (m, 4H), 2.00 (s, 3H), 3.42 (t, 2H), 3.65 (m, 1H), 4.46 (s, 2H), 5.30 (m, 1H), 7.30 (t, 5H), 7.47 (t, 2H), 7.58 (t, 1H), 7.90 (m, 2H). MS (DCI/NH_3) m/e 386 $(M+NH_4)^+$.

Example 70C

Benzyl-[*syn* -(4-acetoxy-5-methyl)-6-hydroxy-6-phenyl]hexyl ether

A solution of the compound resulting from Example 70B (0.5 g, 1.4 mmol), $CeCl_3 \cdot 7\ H_2O$, and 5 mL of MeOH was stirred at 0 °C as $NaBH_4$ (0.16 g, 4.2 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 0.25 hours, then 25 mL of 3 N HCl was added (cautiously), followed by the addition of saturated NaCl solution. The solution was extracted with ether (3x). The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (0.5 g) as a colorless oil (as a mixture of diastereomers). ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (d, 1.5H), 0.97 (d, 1.5 H), 1.57-1.74 (m, 4H), 1.85-1.98 (m, 1H), 2.02 (s, 1.5H), 2.15 (s, 1.5H), 3.45 (t, 1H), 3.51 (m, 1H), 4.12 (dd, 0.5H), 4.50 (d, 2H), 4.75 (m, 0.5H), 4.90 (m, 0.5H), 5.43 (m, 0.5H), 7.32 (m, 10H). MS (DCI/NH_3) m/e 374 $(M+NH_4)^+$.

Example 70D

Benzyl [*syn* -(4-acetoxy-5-methyl)-6-trifluoroacetoxy-6-phenyl]hexyl ether

Trifluoroacetic anhydride (0.2 mL, 1.4 mmol) was added dropwise to a 0 °C solution of the compound resulting from Example 70C (0.5 g, 1.4 mmol), pyridine (0.11 mL), and 7 mL CH_2Cl_2. The reaction mixture was stirred at 0 °C for 4.5 hours then quenched with 0.1 N HCl and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with 0.1 N HCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (0.59 g) as a colorless oil (as a mixture of diastereomers). ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 1.5H), 1.10 (d, 1.5H), 1.50 (m, 1H), 1.64 (m, 2H), 1.78 (m, 1H), 2.02 (d, 3H), 2.32 (m, 1H), 3.39 (t, 1H), 3.50 (m, 2H), 4.98 (d, 2H), 4.67 (m, 0.5H), 5.29 (m, 0.5H), 5.52 (d, 0.5H), 5.78 (d, 0.5H), 7.30 (m, 10H). MS (DCI/NH_3) m/e 470 $(M+NH_4)^+$.

Example 70E

syn -(4-Acetoxy-5-methyl)-6-phenyl-1-hexanol

A mixture of the compound resulting from Example 70D (0.59 g, 1.3 mmol), Pd/C (0.16 g, 10%, dry), and 50 mL of EtOAc was hydrogenated in a Parr shaker at room temperature for 39 hours. The mixture was filtered and concentrated *in vacuo* , and the residue was flash chromatographed on silica gel eluting with 8:2 hexane-EtOAc to afford the title compound (0.18 g) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H), 1.45-1.60 (m, 3H), 1.69 (m, 2H), 2.00 (br s, 1H), 2.09 (s, 3H), 2.33 (dd, 1H), 2.77 (dd,1H), 3.64 (t, 2H), 4.92 (m, 1H), 7.08-7.22 (m, 2H), 7.28 (m, 3H). MS (DCI/NH_3) m/e 268 $(M+NH_4)^+$.

Example 70F

1-Iodo-*syn* -(4-acetoxy-5-methyl)-6-phenylhexane

A solution of the compound resulting from Example 70E (0.33 g, 1.39 mmol) and 9.2 mL anhydrous CH_3CN was stirred at room temperature as the following were added sequentially: imidazole (0.24 g, 3.5 mmol), triphenylphosphine (0.40 g, 1.5 mmol), and iodine (0.39 g, 1.5 mmol). The reaction mixture was stirred at room temperature for 1.25 hours, then H_2O was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated sodium thiosulfate solution and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a white solid. The solid was triturated with hexane (3x), decanting after each. The hexane layers were combined, concentrated *in vacuo* , and the residue obtained flash chromatographed on silica gel eluting with 95:5 hexane-EtOAc to afford the title compound (0.38 g) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.70 (t, 2H), 1.75-1.86 (m, 2H), 1.99 (m, 1H), 2.09 (s, 3H), 2.34 (dd, 1H), 2.77 (dd, 1H), 3.20 (t, 2H), 4.90 (m, 1H), 7.10-7.22 (m, 3H), 7.28 (m, 2H). MS (DCI/NH_3) m/e 378 $(M+NH_4)^+$.

Example 70G

N-Benzyl-N-(t-butyloxycarbonyl)-N-[(*syn* -4-acetoxy-5-methyl)-6-phenylhexyl]amine

A solution of N-benzyl-N-t-butyloxycarbonylamine (0.22 g, 1.05 mmol), prepared by the method described in J. Heterocyclic Chem. 22(5): 1173, (1985), and 0.45 mL of anhydrous DMF was added dropwise to a 0 °C suspension of NaH (0.043 g 1.05 mmol, 60% dispersion, hexane washed) in 1.7 mL of anhyrous DMF. The sodium salt was formed for 0.5 hours at room temperature, then a solution of the compound resulting from Example 70F (0.38 g, 1.05 mmol) in 0.5 mL of anhydrous DMF was added dropwise. The reaction mixture was stirred for 2 days at room temperature. Ice water was added and the solution was extracted (3x) with ethyl acetate. The combined organic layers were washed with H_2O, cold 0.1 N HCl and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (0.46 g) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3H), 1.39-1.57 (m, 13H), 1.92 (br s, 1H), 2.06 (s, 3H), 2.30 (dd, 1H), 2.72 (dd, 1H), 3.18 (br d, 2H), 4.29-4.49 (m, 2H), 4.85 (s, 1H), 7.10 (d, 2H), 7.19-7.38 (m, 8H). MS (DCI/NH_3) m/e 440 $(M+H)^+$, 457 $(M+NH_4)^+$.

Example 70H

N-Benzyl-N-[(*syn* -4-acetoxy-5-methyl)-6-phenylhexyl]amine

Trifluoroacetic acid (7.7 mL) was added to a 0 °C solution of the compound resulting from Example 70G (0.46 g, 1.07 mmol) and 7.7 mL CH_2Cl_2. The reaction was stirred for 0.5 hours at 0 °C and for 1.5 hours at room temperature. The solvent was evaporated *in vacuo* . Toluene was added and evaporated *in vacuo* (2x). Amberlite resin (IRA-400-OH, 0.5 g, washed successively with H_2O, EtOH, ether, and dried) and 15 mL of CH_2Cl_2 was added and the suspension was stirred for 18 hours at room temperature. The suspension was filtered and concentrated *in vacuo* to afford the title compound (0.33 g) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 3H), 1.58 (m, 4H), 1.95 (s, 1H), 2.07 (s, 3H), 2.31 (m, 2H), 2.68 (s, 1H), 2.74 (dd, 2H), 3.82 (s, 2H), 4.85 (m, 1H), 7.08-7.22 (m, 3H), 7.28 (m, 3H), 7.37 (m, 4H). MS (DCI/NH_3) m/e 340 $(M+H)^+$.

Example 70I

5-[N-benzyl-N-{*syn*-(4-acetoxy-5-methyl)-6-phenylhexyl}aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Using the procedures described in Example 4 but substituting the compound resulting from Example 70H for N-benzyl-N-(4-phenoxybenzyl)amine provided the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.63 (d, 3H), 1.16-1.40 (m, 4H), 1.48-1.64 (m, 3H), 1.82 (s, 3H), 2.14-2.38 (m, 1H), 2.89-3.00 (t, 2H), 3.30 (bs, 3H), 4.02-4.15 (m, 1H), 4.63-4.79 (m, 2H), 7.05 (d, 2H), 7.11-7.18 (m, 2H), 7.19-7.38 (m, 8H), 7.46 (d, 2H). MS (FAB) m/e 576(M+H)$^+$.

Example 71

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]pyridine-3-carboxylic acid

A solution of 2,3-pyridinedicarboxylic anhydride (0.365 g, 2.5 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (0.723 g, 2.5 mmol), diisopropylethylamine (0.32 g, 2.5 mmol), and 20 mL of toluene was refluxed for 1 hour, then evaporated under reduced pressure. The residue was taken up in ethyl acetate, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated. The crude product was purified by flash silica gel chromatography eluting with with 95:4:1 $CHCl_3$-MeOH-HOAc to give 0.28 g of the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.18 (d, 2H), 4.55 (d, 2H), 6.80-7.50 (m, 14H), 7.60 (m, 1H), 8.33 (m, 1H), 8.80 (m, 1H). MS (FAB)$^+$ m/e 439 (M+H)$^+$ and (FAB)$^-$ m/e 437 (M-H)$^+$.

Example 72
4,5-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

Example 72A
1,2,4,5-Benzenetetracarboxylic anhydride dichloride

A mixture of 15.0 g (68.8 mmol) of 1,2,4,5-benzenetetracarboxylic dianhydride in 1200 mL of toluene and 90 mL of dimethylformamide was heated to 65 °C under a nitrogen atmosphere, whereupon the compound dissolved. To this solution was added dropwise 35.7 mL (68.8 mmol) of a 1.93 M solution of phosgene in toluene. After maintaining the temperature at 65 °C for 6 hours, most of the volatiles were removed under reduced pressure, affording an oil. The oil crystallized on standing. Further purification was effected by vacuum sublimation.

Example 72B
4,5-Di[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

A solution of 300 mg (1.10 mmol) of the compound resulting from Example 72A and 444 mg (2.20 mmol) of triethylamine in 100 mL of tetrahydrofuran was cooled to -30 °C under a nitrogen atmosphere. To this was added by slow dropwise addition 317 mg (1.10 mmol) of N-benzyl-N-(4-phenoxybenzyl)amine in 30 mL of tetrahydrofuran. After 4 hours at -30 °C the solution was allowed to warm to ambient temperature and stirred for 4 hours. All volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in 50 mL of dichloromethane, and the solution was washed with saturated sodium bicarbonate solution. The solution was dried ($MgSO_4$) and all volatiles were removed under reduced pressure. The oil was dissolved in 50 mL of acetone, and the solution was treated with 50 mL of 1 M HCl. After 24 hours all volatiles were removed under reduced pressure, and the resulting oil was purified by flash column chromatography on silica gel eluting with 180:1:1 followed by 18:1:1 ethyl acetate-formic acid-water to afford 36 mg of the desired

product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.3-4.5 (m, 4H), 4.5-4.7 (m, 4H), 6.8-7.0 (m, 8H), 7.1-7.2 (m, 4H), 7.2-7.5 (m, 18H). MS (FAB)$^+$ m/e 797 (M+H)$^+$.

Example 73

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4-(N-benzylaminocarbonyl)benzene-1,2-dicarboxylic acid

A mixture of 500 mg (2.29 mmol) of 1,2,4,5-benzenetetracarboxylic dianhydride in 20 mL of acetone under an atmosphere of nitrogen was cooled to -30 °C, whereupon a solution of 662 mg (2.29 mmol) of N-benzyl-N-(4-phenoxybenzyl)amine and 296 mg (2.29 mmol) of diisopropylethylamine in 10 mL of acetone was added dropwise. The solution was allowed to warm to ambient temperature. After 24 hours all volatiles were removed under reduced pressure. The resulting oil was dissolved in 50 mL of methylene dichloride, and the solution was washed with dilute hydrochloric acid, dried ($MgSO_4$) and then treated with 1 mL of thionyl chloride. After 6 hours all volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in 20 mL of methylene dichloride and a solution of 245 mg (2.29 mmol) of benzylamine and 296 mg (2.29 mmol) of diisopropylethylamine in 10 mL of methylene dichloride was added dropwise. After 6 hours the mixture was washed with dilute hydrochloric acid, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was dissolved in 50 mL of acetone, and the solution was treated with 50 mL of 1 M HCl. After 24 hours all volatiles were removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with 18:1:1 ethyl acetate-formic acid-water afforded 42 mg of the desired product. ^{1}H NMR (300 MHz, CD_3OD) δ 4.1-4.2 (m, 2H), 4.4-4.5 (m, 2H), 6.7-6.8 (m, 1H), 6.8-6.9 (m, 3H), 6.9-7.1 (m, 3H),7.2-7.4 (m, 14H). MS (FAB)$^+$ m/e 615 (M+H)$^+$.

Example 74a

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzophenone-3',4',4-tricarboxylic acid

and

Example 74b

3',4-Di[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzophenone-3,4'-dicarboxylic acid

To a solution of 1.67 g (5.19 mmol) of 3,3',4,4'-benzophenonetetracarboxylic dianhydride in 100 mL of acetone cooled to 0 °C was added a solution of 1.50 g (5.19 mmol) of N-benzyl-N-(4-phenoxybenzyl)amine and 0.57 g (5.71 mmol) of triethylamine dropwise. The solution was allowed to slowly warm to ambient temperature. After 6 hours all volatiles were removed under reduced pressure, the resulting oil was dissolved in ethyl acetate, and the solution was washed with dilute hydrochloric acid. The solution was then stirred vigorously with 10% hydrochloric acid for 24 hours. The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel eluting with 18:1:1 ethyl acetate-formic acid-water to give 260 mg of 74a and 1.41 g of 74b. Example 74a: ^1H NMR (300 MHz, DMSO-d_6) δ 3.8-3.9 (m, 2H), 4.2-4.3 (m, 2H), 6.8-7.5 (m, 14H), 7.6-8.1 (m, 6H). MS (FAB)$^+$ m/e 630 (M+H)$^+$. Example 74b: ^1H NMR (300 MHz, $CDCl_3$) δ 3.8-3.9 (m, 2H), 4.1-4.3 (m, 4H), 4.8-5.2 (m, 2H), 6.8-7.2 (m, 12H), 7.2-7.4 (m, 12H), 7.5-8.3 (m, 10H). MS (FAB)$^+$ m/e 901 (M+H)$^+$.

Example 75

7-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]naphthalene-2,3,6-tricarboxylic acid

and

Example 76

3,7-Di[N-benzyl-N-(4-phenoxybenzyl)amino-carbonyl]naphthalene-2,6-dicarboxylic acid

2,3,6,7-Naphthalenetetracarboxylic acid dianhydride was prepared using the procedure of Boykin, D.W., Nowak-Wydra, B., and Baumstark, A.L., J. Het. Chem. 28: 609 (1991). The title compounds were prepared by the procedures described in Examples 74a and 74b. Example 75: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.3-4.4 (m, 2H), 4.4-5.0 (bs, 2H), 6.8-7.1 (m, 4H), 7.1-7.5 (m, 12H), 8.24 (d, 1H), 8.69 (d, 1H). MS (FAB)$^+$ m/e 576 (M+H)$^+$. Example 76: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.2-4.3 (m, 4H), 4.4-5.0 (bs, 4H), 6.8-7.1 (m, 9H), 7.1-7.5 (m, 23H), 8.24 (d, 1H), 8.69 (d, 1H). MS (FAB)$^+$ m/e 847 (M+H)$^+$.

Example 77

5-[N-Benzyl-N-(fluoren-2-ylmethyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-(fluoren-2-ylmethyl)amine was prepared by the procedures described for the preparation of N-benzyl-N-(4-phenoxybenzyl)amine. The title compound was prepared in the same manner as Example 74a. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 2H), 4.24 (d, 2H), 4.3-5.0 (bs, 2H), 7.1-7.4 (m, 10H), 7.5-7.7 (m, 2H)7.8-8.1 (m, 2H). MS (FAB)$^+$ m/e 522 (M+H)$^+$.

Example 78

5-[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]-1,3-dimethoxycarbonylbenzene

A slurry of 5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,3-dimethoxycarbonylbenzene (1.03 g, 2.0 mmol) and Lawesson's reagent (404 mg, 1.0 mmol) in THF (7 mL) was stirred at reflux for 18 hours then cooled to room temperature. Silica gel (50 g) was added to the reaction mixture which was then concentrated to dryness. The residue was poured onto a prepacked silica gel column and eluted with 15% ethyl acetate-hexane to provide 927 mg, (88%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58 (s, 3H), 3.59 (s, 3H), 4.6 (d, 2H), 5.4 (d, 2H), 7.0 (m, 8H), 7.4 (m, 6H), 8.2 (m 2H), 8.6 (m, 1H). MS (DCI) m/e 526 $(M+H)^+$.

Example 79

3-Methoxycarbonyl-5-[N-benzyl-N-(4-phenoxybenzyl)aminothio-thiocarbonyl]benzoic acid

A solution of 5-[N-benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]-1,3-dimethoxycarbonylbenzene (716 mg, 1.4 mmol) in THF (21 mL) and water (7 mL) at 0 °C was treated with 1 N LiOH (1.4 mL). After 6 hours at 0 °C and 18 hours at room temperature, the reaction mixture was concentrated to remove THF, acidified to pH 0 with 1 N HCl and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide a yellow solid. The solid was chromatographed eluting with a gradient eluant of 1% MeOH in $CHCl_3$ going to 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 353 mg (50%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.55 (s, 3H), 4.6 (d, 2H), 5.4 (d, 2H), 7.0 (m, 8H), 7.4 (m, 6H), 8.2 (m, 2H), 8.6 (m, 1H), 12.5 (br s, 1H). MS (DCI) m/e 512 $(M+H)^+$.

Example 80

5-[N-Benzyl-N-(4-phenoxybenzyl)aminothiocarbonyl]benzene-1,3-dicarboxylic acid

A solution of the compound resulting from Example 78 (1.18 g, 2.2 mmol) in THF (45 mL) and water (33 mL) was treated with 1 N LiOH (13.4 mL). After 18 hours the THF was removed, and the aqueous solution was acidified to pH 0 with 1 N HCl and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide a yellow solid. The solid was chromatographed eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 97 mg (87%) of the title compound as a yellow solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.7 (d, 2H), 5.5 (d, 2H), 7.0 (m, 8H), 7.4 (m, 6H), 8.2 (m, 2H), 8.6 (m, 1H), 12.5 (br s, 2H). MS (FAB) m/e 498 $(M+H)^+$.

Example 81

N-Benzyl-N-(3,5-dimethoxycarbonylbenzyl)-N-(4-phenoxybenzyl)amine

A slurry of the compound resulting from Example 78 (2 g, 3.8 mmol) and Raney nickel (4.5 g, 77 mmol) in methanol (50 mL) was stirred for 18 hours at room temperature then filtered through celite. The filtrate was concentrated *in vacuo* and chromatographed eluting with 10% ethyl acetate in hexane to provide 483 mg (26%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 2H), 3.56 (s, 2H), 3.65 (s, 2H), 3.95 (m, 6H), 6.9-7.1 (m, 6H), 7.2-7.45 (m, 8H), 8.25 (s, 2H), 8.55 (s, 1H). MS (DCI) m/e 496 $(M+H)^+$.

Example 82

5-[N-Benzyl-N-(4-phenoxybenzyl)aminomethyl]benzene-1,3-dicarboxylic acid disodium salt

A solution of the compound resulting from Example 78 (1.1 g, 2.16 mmol) and NaOH (173 mg, 4.32 mmol) in water (7 mL) at room temperature was treated with Raney nickel (2.5 g, 43.2 mmol) and stirred for 18 hours. The solution was filtered through celite and then lyophilized. The resulting white solid was redissolved in water and gradient eluted through a C_{18} reversed phase column eluting with water with an increasing CH_3CN concentration to provide 871 mg (79%) of the title compound as a white solid. ^1H NMR (D_2O,

300 MHz) δ 3.6 (d, 2H), 4.8 (d, 2H), 5.4 (d, 2H), 6.8-7.1 (m, 7H), 7.2-7.45 (m, 7 H), 7.8 (dd, 1H), 7.9 (dd, 1H), 8.2 (dd, 1H). MS (FAB) m/e 512 $[M+H, (diacid)]^+$.

Example 83

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,4-dimethoxycarbonylbenzene

Example 83A

2,5-Dimethoxycarbonylbenzoic acid

A slurry of dimethyl iodoterephthalate and sodium acetate in 1:1 DMF-H_2O (56 mL) was treated with palladium acetate (32 mg) and stirred at 50 °C for 18 hours under an atmosphere of carbon monoxide. The solution was acidified to pH 0 and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide an oil. Chromatography of the oil eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid provided 200 mg (6%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 3H), 4.0 (s, 3H), 7.75 (d, 1H), 8.3 (dd, 1H), 8.6 (d, 1H), 11.2 (br s, 1H). MS (DCI) m/e 239 $(M+H)^+$.

Example 83B

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,4-dimethoxycarbonylbenzene

A solution of the compound resulting from Example 83A (42 mg, 0.18 mmol) in toluene (1 mL) was treated with oxalyl chloride (25 mg, 0.19 mmol) and DMF (2 drops). After 18 hours, the solution was concentrated to dryness, and the 2,5-dimethoxycarbonylbenzoyl chloride thus obtained was dissolved in CH_2Cl_2 and added dropwise to a slurry of N-benzyl-N-(4-phenoxybenzyl)amine hydrochloride (117 mg, 0.36 mmol) and $NaHCO_3$ (151 mg, 1.8 mmol) in water (3 mL). After 18 hours, the CH_2Cl_2 layer was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 89 mg (98%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.8 (d, 2H),

3.79 (d, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.2 (d, 2H), 6.9-7.15 (m, 7H), 7.25-7.45 (m, 5H), 8.0-8.1 (m, 3H). MS (DCI) 510 $(M+H)^+$.

Example 84

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,4-dicarboxylic acid

A solution of the compound resulting from Example 83 (25 mg, 0.049 mmol) in THF (750 µL) and water (250 µL) was treated with 1 N LiOH (290 µL). After 18 hours, the solution was acidified to pH 0 with 1 N HCl, concentrated to remove THF and extracted with ethyl acetate (2 x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated, and the residue was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 23 mg (98%) of the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.09 (s, 2H), 4.11 (s, 2H), 6.9-7.25 (m, 14H), 7.8 (d, 1H), 8.0 (m, 2H), 13.5 (br s, 2H). MS (FAB) m/e 482 $(M+H)^+$.

Example 85

2-[N-(4-phenoxybenzyl)carbonylamino]-1,4-dimethoxycarbonylbenzene

4-Phenoxyphenylacetic acid (1 g, 4.4 mmol) in toluene (15 mL) was treated with oxalyl chloride (614 mg, 4.84 mmol) and DMF (2 drops). After 18 hours, the reaction was concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (20 mL) and added to a suspension of dimethyl aminoterephthalate (920 mg, 4.4 mmol) and $NaHCO_3$ (4.7 mg, 44 mmol) in water (30 mL). After 18 hours, the methylene chloride was dried ($MgSO_4$), filtered and concentrated to provide a yellow solid which was chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 1.4 g (76%) of the title compound as a white solid. ^1H NMR δ 3.8 (s, 2H), 3.95 (s, 3H), 3.96 (s, 3H), 7.05 (m, 5H), 7.35 (m, 4H), 7.75 (dd, 1H), 8.1 (d, 1H), 9.35 (d, 1H), 11.0 (br s, 1H). MS (DCI) m/e 420 $(M+H)^+$.

Example 86

2-[N-(4-Phenoxybenzyl)carbonylamino]benzene-1,4-dicarboxylic acid

The compound resulting from Example 85 (620 mg, 1.5 mmol) in methanol (7 mL) and water (7 mL) was treated with 87 % KOH (954 mg, 14.8 mmol). After 18 hours, the solution was acidified to pH 0 with 1 N HCl and concentrated to remove the methanol. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 563 mg (97%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 2H), 7.0 (m, 3H), 7.15 (m, 2H), 7.4 (m, 4H), 7.65 (dd, 1H), 8.1 (d, 1H), 9.1 (d, 1H), 11.1 (br s, 1H), 13.3 (br s, 2H). MS (DCI) m/e 409 $(M+NH_4)^+$.

Example 87

4-[N-Benzyl-N-(4-phenoxybenzyl)carbonylamino]-1,2-dimethoxycarbonylbenzene

Example 87A

Dimethyl 4-aminophthalate

A slurry of dimethyl 4-nitrophthalate (5.37 g, 22.5 mmol) and ammonium formate 1.42 g, 225 mmol) in methanol (75 mL) was treated with 10% palladium on carbon (500 mg), and the resulting mixture was stirred at reflux for 3 hours. The reaction mixture was cooled, filtered through celite and concentrated to provide the title compound as a white solid used directly in the next step. ^1HNMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 3H), 3.9 (s, 3H), 4.2 (br s, 2H), 6.65 (dd, 1H), 6.7 (d, 1H), 7.7 (d, 1H). MS (DCI) m/e 210 $(M+H)^+$.

Example 87B

4-[N-(4-Phenoxybenzyl)carbonylamino]-1,2-dimethoxycarbonylbenzene

4-Phenoxyphenylacetic acid (1g, 4.4 mmol) in toluene (15 mL) was treated with oxalyl chloride (614 mg, 4.8 mmol) and DMF (2 drops). After 18 hours, the reaction was concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (20 mL) and added dropwise to a slurry of $NaHCO_3$ (4.64 g, 43.8 mmol) and the compound resulting from Example 87A (920 mg, 4.4 mmol) in water (30 mL). After 18 hours, the methylene chloride layer was dried ($MgSO_4$), filtered and concentrated, and the residue was chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 1.2 g (65 %) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.9 (s, 3H), 4.0 (s, 3H), 4.5 (br s, 1H), 4.6 (d, 2H), 6.8-7.7 (m, 11H), 7.7 (d, 1H). MS (DCI) m/e 420 $(M+H)^+$.

Example 87C

4-[N-Benzyl-N-(4-phenoxybenzyl)carbonylamino]-1,2-dimethoxycarbonylbenzene

A slurry of benzyl bromide (558 mg, 3.3 mmol) and 60 % sodium hydride (65 mg, 1.6 mmol) in DMF (10 mL) was treated with the compound resulting from Example 87B (639 mg, 1.6 mmol) and stirred for 18 hours at room temperature. Water (20 mL) was added, and the suspension was extracted with ethyl acetate (3 x 20 mL). The ethyl acetate was dried ($MgSO_4$), filtered and concentrated to provide a residue which was chromatographed on silica gel eluting with 15 % ethyl acetate in hexane to provide 722 mg (87 %) the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.9 (s, 3H), 4.0 (s, 3H), 4.6 (d, 2H), 5.2 (d, 2H), 6.8-7.7 (m, 16H), 7.7 (d, 1H). MS (DCI) m/e 510 $(M+H)^+$.

Example 88

3-Methansulfonylamino-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid

Example 88A

3-Nitro-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid methyl ester

To a stirred suspension of 3-nitroisophthalic acid monomethyl ester (2.25 g, 10 mmol, 1.0 eq.) in 50 mL of CH_2Cl_2 was added 1.05 mL (12 mmol, 1.2 eq.) of oxalyl chloride followed by 3 drops of DMF. The solution was stirred at room temperature for 2 hours and concentrated to dryness. The resulting white solid was redissolved in 25 mL of CH_2Cl_2 and 3.42 g (10.5 mmol, 1.05 eq.) of N-benzyl-N-(4-phenoxybenzyl)amine · HCl was added, and the suspension was cooled to 0 °C. Triethylamine (4.2 mL, 30 mmol, 3 eq.) was added dropwise, and the resulting solution was stirred overnight while the ice bath melted. The mixture was poured into a separatory funnel and extracted with water, 3 N aqueous HCl, dried, filtered and concentrated to give the title compound (5.04 g, 101%) as a thick oil. ^{1}H NMR (300MHz., $CDCl_3$) δ 7.50 (t, 1H), 7.20 - 7.44 (m, 8H), 7.13 (m, 3H), 7.04 (m, 5H), 4.69 (bd, 2H), 4.43 (bd, 2H), 3.89 (s, 3H). MS (DCI, NH_3) m/e 514 (8%); 290 (100%).

Example 88B

3-Amino-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid methyl ester

To a stirred solution of 2.48 g (5 mmol, 1.0 eq.) of the compound resulting from Example 88A in 40 mL of methanol was added 500 mg of 10% Pd/C followed by 1.58 g (25 mmol, 5 eq.) of $NH_4^+HCO_2^-$, and the mixture was heated to reflux for 1 hour and then cooled to room temperature. The suspension was diluted with ethyl ether and filtered through a plug of SiO_2 (prewetted with ether) and the pad washed well with ether. The filtrate was concentrated to give 1.94 g (83%) of the title compound as a white foam. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.86 (t, 1H), 8.47 (m, 1H), 8.43 (t, 1H), 7.37 (m, 7H), 7.12 (m, 2H), 7.01 (m, 5H), 4.73

(bd, 2H), 4.41 (bd, 2H), 3.98 (s, 3H). MS (DCI, NH_3) m/e 484 (25%); 467 (100%).

Example 88C

3-Methansulfonylamino-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid methyl ester

To a stirred solution of 233 mg (0.5 mmol, 1.0 eq) of the compound resulting from Example 88B in 5 mL of CH_2Cl_2 at 0 °C was added 0.12 mL (1.0 mmol, 2.0 eq.) of 2,6-lutidine follwed by the addition of 42 µL (0.55 mmol, 1.1 eq.) of methanesulfonyl chloride. After stirring for 48 hours, the mixture was diluted with CH_2Cl_2 and extracted with 3 N aqueous HCl, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 40% ethyl acetate in hexanes to give 162 mg (60%) of the title compound as a white foam. ^1H NMR (300MHz., $CDCl_3$) δ 7.93 (t, 1H), 7.88 (bs, 1H), 7.57 (bs, 1H), 7.22 - 7.42 (m, 7H), 7.13 (m, 2H), 7.04 (m, 5H), 4.71 (bd, 2H), 4.39 (bd, 2H), 3.91 (bs, 3H), 3.97 and 3.92 (2s, 3H). MS (DCI, NH_3) m/e 562 (100%); 545 (20%); 453 (25%); 290 (38%).

Example 88D

3-Methansulfonylamino-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzoic acid

The title compound was prepared as a white lyophilate from the compound resulting from Example 88C and using the procedures described in Example 116B. ^1H NMR (300MHz., DMSO-d_6): δ 11.1 (s, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 7.47 (t, 1H), 7.24 - 7.43 (m, 7H), 7.14 (m, 3H), 6.99 (m, 4H), 4.62 (bd, 2H), 4.43 (bs, 2H), 2.96 (bs, 3H). MS (DCI, NH_3) m/e 548 (75%); 531 (50%); 381 (20%); 366 (100%); 349 (20%); 200 (16%); 183 (20%). Anal calcd for $C_{29}H_{26}N_2O_6S \cdot 0.49\ H_20$: C, 65.65; H, 4.94; N, 5.28. Found: C, 64.58; H, 4.99; N, 5.40.

Example 89

4-[N-Benzyl-N-(4-phenoxybenzylcarbonyl)amino]benzene-1,2-dicarboxylic acid

A solution of the compound resulting from Example 87 (310 mg, 0.61 mmol) in methanol (3 mL) and water (3 mL) was treated with 87 % KOH (34 mg, 6.1 mmol) and stirred for 18 hours at room temperature. The solution was acidified to pH 0 with 1 N HCl, concentrated to remove methanol and extracted with ethyl acetate (2 x 10 mL). The ethyl acetate was dried ($MgSO_4$), filtered and concentrated to provide a residue which was chromatographed eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 287 mg (98 %) of the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.5 (d, 2H), 5.1 (d, 2H), 6.8-7.5 (m, 16H), 7.6 (d, 1H), 13.4 (br s, 2H). MS (FAB) m/e 482 $(M+H)^+$.

Example 90

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]-1,4-dimethoxycarbonylbenzene

A solution of 2,5-dimethoxycarbonylbenzoic acid (100 mg, 0.42 mmol) in toluene (2 mL) was treated with diphenylphosphoryl azide (127 mg, 0.46 mmol) and triethylamine (85 mg, 0.84 mmol) then warmed to 80 °C for 18 hours. N-Benzyl-N-(4-phenoxybenzyl)amine hydrochloride (137 mg, 0.42 mmol) was added, and the brown mixture was stirred an additional 18 hours. Volatiles were removed, and the residue was dissolved in ethyl acetate (5 mL) and washed with 1 N HCl (5 mL), half saturated $NaHCO_3$ (5 mL) and brine (5 mL). The ethyl acetate layer was dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 190 mg (86%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.9 (s, 3H), 3.91 (s, 3H), 4.4 (d, 2H), 4.6 (d, 2H), 5.8 (br s, 1H), 6.8-7.7 (m, 16H), 7.9 (d, 1H). MS (DCI) m/e 525 $(M+H)^+$.

Example 91

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,4-dicarboxylic acid

The compound resulting from Example 90 (17.4 mg, 0.03 mmol) in water (500 µL) and THF (166 µL) at room temperature was treated with 1 N LiOH (330 µL) and stirred for 18 hours. The solution was acidified to pH 0 with 1 N HCl and concentrated to remove THF. The water layer was extracted with ethyl acetate (1 mL). The ethyl acetate was dried ($MgSO_4$), filtered and concentrated to provide a residue which was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-acetic acid to provide 10.1 mg (62%) of the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.5 (d, 2H), 4.6 (d, 2H), 5.(br s, 1H), 6.5-7.6 (m, 16H), 7.9 (d, 1H), 12.5 (br s, 2H). MS (FAB) m/e 497 $(M+H)^+$.

Example 92

5-{N-Benzyl-N-[2,4-di(4-chlorophenoxy)benzyl]aminocarbonyl}benzene-1,2,4-tricarboxylic acid

Example 92A

2,4-Di(4-chlorophenoxy)benzonitrile

A mixture of 2,4-difluorobenzonitrile (2.68 g, 20 mmol), 4-chlorophenol (7.72 g, 60 mmol), and anhydrous potassium carbonate (8.29 g, 60 mmol) in anhydrous DMF (60 mL) was refluxed 15 hours. The reaction mixture was then poured to a separation funnel containing water (50 mL) and ether (300 mL). The organic layer was separated and was further washed with aqueous sodium hydroxide (2.0 M, 20 mL), water (40 mL), half saturated ammonium chloride (50 mL), and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then redissolved in a minimum amount of hot ethyl acetate and then gradually cooled to 0 °C. The crystals were collected by suction filtration, washed with cold ether, and air dried to give the title compound (5.87 g, 80%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1 H), 7.36 (m, 4 H), 7.04 (dt, 2 H), 6.97 (dt, 2 H), 6.62 (dd, 1 H), 6.47 (d, 1 H).

Example 92B

2,4-Di(4-chlorophenoxy)benzylamine hydrochloride

To a 0 °C solution of the compound resulting from Example 92A (5.83 g, 16.4 mmol) in THF (40 mL) was added slowly a solution of lithium aluminum hydride (1.0 M in THF, 16.4 mmol). The reaction mixture was reluxed for 5 hours and then cooled to 0 °C. To it was slowly added water (0.65 mL), 15% aqueous NaOH (0.65 mL), and water (2 mL), and the mixture was stirred at 25 °C for 30 minutes, and then filtered through Celite. The filtrate was concentrated, redissolved in ether (50 mL), and cooled to 0 °C. Concentrated hydrochloric acid (2 mL) was then added dropwise to the mixture with good stirring. The white precipitate was collected by suction filtration and dried under high vacuum to give the title compound as a HCl salt (5.75 g, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (br. s., 3H), 7.59 (d, 1H), 7.50 (dt, 2H), 7.45 (dt, 2H), 7.15 (dt, 2H), 7.04 (dt, 2H), 6.83 (dd, 1H), 6.48 (d, 1H), 4.04 (q, 2H).

Example 92C

N-Benzyl-N-[2,4-di(4-chlorophenoxy)benzyl]amine

The compound resulting from Example 92B (799 mg, 2.0 mmol) was mixed with benzaldehyde (203 µL, 2.0 mmol) in ethanol (5 mL). After 1 hour, acetic acid (200 mg), sodium acetate (300 mg), and sodium cyanoborohydride (1.0 M in THF, 2.0 mL) was added to the mixture. After 15 hours, concentrated hydrochloric acid (0.5 mL) was slowly added to the reaction mixture, followed by addition of 20% aqueous NaOH (8 mL) over 10 minutes. The mixture was then diluted with ether (80 mL), washed with water and brine, dried over anhydrous potassium carbonate, filtered, and concentrated *in vacuo*. The residue was then purified with column chromatography eluting with 50% ether in hexane to give the title compound (507 mg, 56%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42-7.22 (m, 10H), 6.92 (d, 2H), 6.87 (d, 2H), 6.74 (d, 1H), 6.53 (s, 1H), 3.79 (s, 4H).

Example 92D

5-{N-Benzyl-N-[2,4-di(4-chlorphenoxy)benzyl]aminocarbonyl}benzene-1,2,4-tricarboxylic acid

Using the procedure described in Example 4 and the compound resulting from Example 92C the title compound was obtained in 42% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30, 8.22,8.00, 7.94 (4 singlets, 2H), 7.73-6.63 (m, 15H), 6.52, 6.48 (2 triplets, 1H), 4.31, 4.09 (2 br. singlets, 4H). MS (FAB -) m/e 684 (M-H).

Example 93

(±)-5-[N-(Indan-2-yl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 93A

(±)-N-(Indan-2-yl)-N-(4-phenoxy)benzylamine

The procedure described in Example 92C was used to combine (±)-2-aminoindane (266 mg, 2 mmol) and 4-phenoxybenzaldehyde (396 mg, 2 mmol) to give the title compound (628 mg, 100%) without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-6.97 (m, 13H), 4.33 (t, 1H), 3.91 (d, 1H), 3.87 (d, 1H), 3.05 (m, 1H), 2.82 (m, 1H), 2.44 (m, 1H), 1.94 (m, 1H).

Example 93B

(±)-5-[N-(Indan-2-yl)-N-(4-phenoxy)benzylaminocarbonyl]benzene-1,2,4-tricarboxylic acid

The procedure decribed in Example 4 was used to react the compound resulting from Example 93A (2 mmol) and 1,2,4,5-benzenetetracarboxylic dianhydride (2 mmol) to give the title compound (757 mg, 69%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 and 8.29 (2 singlets, 1H), 7.98 and 7.83 (2 singlets, 1H), 7.44-6.74 (m, 13H), 5.11 (t, 1H), 4.80-4.60 and 4.30-4.10 (2 m's, 2H), 2.80 and 2.70 (2 m's, 2H), 2.18 and 1.95 (2 m's, 2H). MS (FAB-) m/e 550 (M-H).

Example 94

(±)-5-[N-(Indan-1-yl)-N-(4-phenoxy)benzylaminocarbonyl]benzene-1,2,4-tricarboxylic acid

The title compound was prepared by the procedures described in Example 93 starting with 1-aminoindane instead of the (±)-2-aminoindane compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60-8.00 (4 singlets, 2 H), 7.43-6.90 (m, 13 H), 4.80-4.60 (2 br. singlets, 2 H), 4.35 (m, 1 H), 3.35-2.80 (m, 4 H). MS (FAB-) m/e 550 (M-H).

Example 95

5-[N-((±)-α-Carbomethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 95A

N-((±)-α-Carbomethoxybenzyl)-N-(4-phenoxybenzyl)amine

The procedure described in Example 92C was used to combine (±)-phenylglycine (4.03 g, 20 mmol) and 4-phenoxybenzaldehyde (3.88 g, 19.6 mmol) to give the title compound (5.51 g, 79%), after column purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 9 H), 7.10 (m, 1 H), 7.02-6.95 (m, 4 H), 4.41 (s, 1 H), 3.70 (s, 5 H).

Example 95B

5-[N-((±)-α-Carbomethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The procedures decribed in Example 4 were used to react the compound resulting from Example 95A (347 mg, 1 mmol) and 1,2,4,5-benzenetetracarboxylic dianhydride (262 mg, 1.2 mmol) to give the title compound (491 mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 and 8.74 and 8.18 and 8.16 (4 singlets, 2H), 7.50 -6.60 (m, 14H), 5.30 (br. s., 1H), 4.38-4.00 (m, 2H), 3.73 and 3.67 (2 singlets, 3H). MS (FAB -) m/e 582 (M-H).

Example 96

4-[N-((±)-α-Carbomethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

To a solution of trimellitic anhydride chloride (505 mg, 2.4 mmol) at 0 °C was added a solution of the compound resulting from Example 95A (695 mg, 2.0 mmol) over 1.5 hours. After another 15 hours, the reaction was quenched with aqueous 10% sodium carbonate (10 mL). After 30 minutes, the mixture was acidified with aqueous 3 N hydrochloric acid to pH ~2. The resulting mixture was extracted with ethyl acetate (2 x 60 mL), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 94:5:1 ethyl acetate-methanol-formic acid to give the title compound (917 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00-6.90 (m, 17H), 5.70 (br. s, 1H), 4.60-4.35 (m, 2H), 3.70 (br. s, 3H). MS (FAB -) m/e 538 (M-H).

Example 97

4-[N-((±)-α-Carboxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

A mixture of the compound resulting from Example 96 (323 mg, 0.60 mmol) and aqueous NaOH (2 N, 1 mL) in THF (3 mL) was stirred at room temperature for 72 hours. The mixture was then acidified with aqueous 3 N HCl (1 mL) and extracted (4 x 20 mL) with 1:4 methanol-dichloromethane mixed solvent. The combined extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with 95:5:2 ethyl acetate-methanol-formic acid to give the title compound (297 mg, 95 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80-6.93 (m, 17 H), 5.65 (br. s, 1 H), 4.60-4.35 (m, 2 H). MS (FAB -) m/e 524 (M-H).

Example 98

4-[3-Phenyl-2-(4-phenoxybenzyl)propionyl]benzene-1,2-dicarboxylic acid

Example 98A

Dimethyl 4-vinylphthalate

To a solution of dimethyl 4-hydroxyphthalate (2.10 g, 10.0 mmol) and pyridine (1.6 mL, 20 mmol) in dichloromethane (20 mL) at -78 °C was added slowly trifluoromethanesulfonic anhydride (2.02 mL, 12 mmol). After the reaction was allowed to warm to room temperature overnight, it was diluted with ether (80 mL), washed with water, saturated copper(II) sulfate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 20% ethyl acetate in hexane to give the desired triflate (3.37 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, 1H), 7.66 (d, 1H), 7.48 (dd, 1H), 3.66 (s, 3H), 3.64 (s, 3H).

A mixture of the triflate (2.39 g, 7.0 mmol), lithium chloride (0.88 g, 21 mmol), vinyltributyltin (2.66 g, 8.4 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.243 g, 0.21 mmol) in degassed anhydrous 1,4-dioxane (20 mL) was heated at 90 ° for 8 hours. The mixture was then filtered through silica gel (20 g) and concentrated. The residue was redissolved in ether (80 mL), and water (0.2 mL) was added. To this mixture was added DBU (2 mL) dropwise, and then the mixture was filtered through silica gel (20 g). The residue after concentration of the filtrate was purified by column chromatography eluting with 5% ether in hexane (200 mL) followed by 10% ethyl acetate in hexane to give the title compound (1.01 g, 66%) contaminated with small amount of tributyltin derivatives. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 1H), 7.71 (d, 1H), 7.55 (dd, 1H), 6.73 (dd, 1H), 5.88 (d, 1H), 5.42 (d, 1H), 3.93 (s, 3H), 3.91 (s, 3H).

Example 98B

Dimethyl 4-formylphthalate

A mixture of the compound resulting from Example 98A (1.01 g, 4.6 mmol), osmium tetraoxide (5 mg/mL solution in *t*-butanol, 10 mL, 0.2 mmol), and sodium periodate (5.74 g, 27 mmol) in 2:1 1,4-dioxane-water (30 mL) was stirred 4 hours. The resulting mixture was filtered through celite, rinsed with 1:1 ethyl acetate-ether (90 mL). The filtrate was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 15% ethyl acetate in hexane to give the title compound (0.948 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1 H), 8.60 (d, 1 H), 8.07 (dd, 1 H), 7.84 (d, 1 H), 3.96 (s, 6 H).

Example 98C

Dimethyl 4-[3-(*para*-phenoxyphenyl)propionyl]phthalate

To a solution of 4-phenoxyphenylacetic acid (2.28 g, 10 mmol) in THF (30 mL) was added lithium aluminum hydride (1.0 M in THF, 10 mL) cautiously. After 4 hours at room temperature, the reaction was cooled to 0 °C, and water (0.4 mL), aqueous 15% NaOH (0.4 mL) and water (1.2 mL) were added sequentially. The resulting muddy mixture was filtered through celite and concentrated to give 1(4'-phenoxyphenyl)-1-ethanol (1.42 g). The alcohol was dissolved in dichloromethane (20 mL), and to this solution was added carbon tetrabromide (2.65 g, 8.0 mmol) in one portion and triphenylphosphine (2.10 g, 8.0 mmol) in 3 equal portions (at 2 minute intervals). After 6 hours, the mixture was diluted with hexane (30 mL), and the mixture was filtered through silica gel (20 g), rinsed with 1:2 ether-hexane (50 mL). The residue after concentration of the filtrate was purified by column chromatography eluting with 5% ethyl acetate in hexane to give 1-(4'-phenoxyphenyl)-2-ethyl bromide (1.67 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-6.95 (m, 9 H), 3.57 (t, 2 H), 3.14 (t, 2 H).

A THF (10 mL) solution of the bromide prepared above (1.67 g, 6.02 mmol) in an addition funnel was added to a flask containing magnesium (0.29 g, 12 mmol) and a crystal of iodine. After the reaction was initiated, the addition rate was adjusted so that the reaction was smoothly refluxed. The reaction was

refluxed for 1 hour after completion of the bromide addition to afford the Grignard reagent, 1-(4-phenoxyphenyl)-2-ethylmagnesium bromide. Titration of the solution with n-propanol (1,10-phenantholine as indicator) found that the solution to be 0.55 M.

To a solution of the aldehyde prepared in Example 98B (1.35 g, 6.1 mmol) in THF (10 mL) at -78 °C was added slowly the Grignard solution (10 mL, 5.5 mmol). The reaction was warmed to room temperature over 30 minutes and quenched with saturated ammonium chloride (5 mL). The resulting mixture was diluted with ether to 100 mL, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% followed by 50 % ethyl acetate in hexane to give the desired dimethyl 4-[3-(*para*-phenoxyphenyl)-1-hydroxypropyl]phthalate as the first fraction (1.32 g, 57%), and dimethyl 4-hydroxymethylphthalate as the second fraction (0.46 g, 34%). ^{1}H NMR of the desired secondary alcohol (300 MHz, $CDCl_3$) δ 7.75 (d, 1H), 7.69 (d, 1H), 7.53 (dd, 1H), 7.32 (t, 2H), 7.15 (d, 2H), 7.09 (dt, 1H), 6.99 (d, 2H), 6.94 (d, 2H), 4.79 (m, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.71 (m, 2H), 2.06 (m, 2H), 1.95 (d, 1H).

To a mixture of the above secondary alcohol (1.32 g, 3.14 mmol), activated powdered molecular sieves 4 Å (2 g) in dichloromethane (25 mL) at 0 °C was added pyridinium chlorochromate (1.38 g, 6.28 mmol). After 1 hour, the reaction was diluted with ether (25 mL) and filtered through silica gel. Concentration of the filtrate yielded the title compound (1.08 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, 1 H), 8.13 (dd, 1H), 7.78 (d, 1H), 7.37-6.92 (m, 9H), 3.95 (s , 6H), 3.33 (t, 2H), 3.07 (t, 2H).

Example 98D

4-[3-Phenyl-2-(4-phenoxybenzyl)propionyl]-1,2-dimethoxycarbonylbenzene

To a solution of the compound resulting from Example 98C (491 mg, 1.17 mmol) in THF (10 mL) was added potassium hexamethyldisilazide (0.5 M in toluene, 2.8 mL). After 30 minutes, benzyl bromide (167 µL, 1.41 mmol) was added to the reaction, and the reaction was allowed to warm to room temperature over 15 hours. The reaction was quenched with saturated ammonium chloride (5 mL), diluted with ether to 80 mL, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 20% ethyl acetate in hexane to give the title compound (470 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.83-6.82 (m, 9H), 3.95 (m, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.10 (m, 2H), 2.88 (dt, 2H).

Example 98E

4-[3-Phenyl-2-(4-phenoxybenzyl)propionyl]benzene-1,2-dicarboxylic acid

A mixture of the compound resulting from Example 98D (69 mg) and aqueous 2 N NaOH (1 mL) in THF (3 mL) was refluxed 12 hours. The reaction mixture was then acidified with aqueous 3 N hydrochloric acid (1 mL), diluted with ethyl acetate to 50 mL, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 95:4:1 ethyl acetate-methanol-formic acid to give the title compound (61.5 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.03 (d, 1H), 7.85 (dd, 1H), 7.32-7.06 (m, 10H), 6.80 (d, 2H), 6.78 (d, 2H).4.29 (m, 1H), 3.04 (dd, 1H), 2.95 (dd, 1H), 2.85 (m, 2H). MS (DCI) m/e, 480 ($M-H_2O+NH_4^+$), 498 ($M+NH_4^+$).

Example 99
4-[2-Benzyl-1-hydroxy-3-(4-phenoxyphenyl)propyl]benzene-1,2-dicarboxylic acid

Example 99A
4-[2-Benzyl-1-hydroxy-3-(4-phenoxyphenyl)propyl]-1,2-dimethoxycarbonylbenzene

To a solution of the compound resulting from Example 98D (389 mg, 0.76 mmol) in ethanol (5 mL) at 0 °C was added sodium borohydride (58 mg, 1.53 mmol) in two equal portions. The reaction mixture was then stirred at room temperature for 1 hour and poured to a separatory funnel containing ether (80 mL) and half saturated ammonium chloride (10 mL). The orgainc layer was separated and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (311 mg, 79%) as a mixture of diastereomers (~1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (2 doublets, 1H), 7.63 (2 doublets, 1H), 7.48 (m, 1H), 7.34-6.87 (m, 14H), 4.78 (m, 1H), 3.91 (3 singlets, 6H), 2.70 (m, 2H), 2.58 (m, 2H), 2.32 (m, 1H), 1.89 (d, 1H).

Example 99B
4-[2-Benzyl-1-hydroxy-3-(4-phenoxyphenyl)propyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 98E and the compound resulting from Example 99A (56 mg, 0.11 mmol) afforded the title compound (50 mg, 94%) as a mixture of 1:1 diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (m, 2H), 7.43 (m, 1H), 7.39-6.82 (m, 14H), 4.80 (m, 1H), 2.75 (m, 1H), 2.48 (m, 2H), 2.39 (m, 1H), 2.25 (m, 1H). MS (DCI) m/e, 482 ($M-H_2O+NH_4^+$), 500 ($M+NH_4^+$).

Example 100

4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 100A

Dimethyl (*cis & trans*)-4-[2-benzyl-3-(4-phenoxyphenyl)-propen-1-yl]phthalate

To a solution of the compound resulting from Example 99A (208 mg, 0.41 mmol) and pyridine (0. 6 mL) in dichloromethane (5 mL) at 0 °C was added phosphorus oxychloride (0.3 mL) dropwise, follwed by DBU (0.2 mL). After the reaction mixture was stirred at room temperature for 2 hours, it was diluted with 1:1 ether-hexane (20 mL), filtered through silica gel, and rinsed with ether. The residue after concentration of the filtrate was purified by column chromatography eluting with 20% ethyl acetate in hexane to give the title compound (31 mg, 15%) as a mixture of 1:1 trans/cis isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.47 (m, 3H), 7.36-6.88 (m, 14H), 4.98 (m, 1H), 3.92 (3 singlets, 6H), 2.66 (m, 4H).

Example 100B

(cis & trans)-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure decribed in Example 98E and the compound resulting from Example 100A (30 mg) afforded the title compound (13 mg, 51%) as a mixture of 1:1 trans/cis isomers. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80-6.83 (m, 17H), 5.59 & 4.61 (2 doublets, 1H), 2.80-2.30 (m, 4H). MS (DCI) m/e, 464 (M-H_2O+NH_4^+), 482 (M+NH_4^+).

Example 101

4-[N-Benzyl-N-(4-phenoxybenzyl)aminomethyl]benzene-1,2-dicarboxylic acid

Example 101A

Dimethyl 4-[N-benzyl-N-(*para*-phenoxy)benzylaminomethyl]phthalate

A solution of the compound resulting from Example 98B (228 mg, 1.02 mmol), N-benzyl-N-(4-phenoxy)benzylamine hydrochloride (332 mg, 1.02 mmol), sodium cyanoborohydride (1.0 M in THF, 1.0 mL), and acetic acid (0.3 mL) in ethanol was stirred at room temperature for 15 hours. The reaction mixture was then diluted with ethyl acetate (80 mL), washed with 15% aqueous NaOH (10 mL), saturated sodium bicarbonate (10 mL), water (10 mL), and brine, dried over anhydrous potassium carbonate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography to give the title compound (510 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 1H), 7.70 (s, 1H), 7.59 (d, 1H), 7.40-6.95 (m, 14H), 3.92 (s, 3H), 3.90 (s, 3H), 3.61 (s, 1H), 3.56 (s, 2H), 3.52 (s, 2H).

Example 101B

4-[N-Benzyl-N-(4-phenoxybenzyl)aminomethyl]benzene-1,2-dicarboxylic acid

A mixture of the compound resulting from Example 101A (512 mg, 1.03 mmol), aqueous 2 N NaOH (2 mL) in THF (5 mL) was refluxed 12 hours. To the reaction mixture was added 4 N hydrogen chloride in 1,4-dioxane (2 mL) and silica gel (1 g), and the mixture was evaporated to dryness. The residue was suspended in chloroform, and the slurry was loaded to a column packed with silica gel. The column was eluted sequentially with 3% methanol in ethyl acetate followed by 94:5:1 ethyl acetate-methanol-formic acid to give the title compound (458 mg, 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.90 (br singlet, 2H), 9.95 (br. singlet 1H), 7.90 (m, 2H), 7.63 (m, 5H), 7.15 (t, 1H), 7.00 (d, 2H), 6.93 (d, 2H). MS (DCI) m/e, 468 $(M+H)^+$, 450 $(M-H_2O+H)^+$.

Example 102a

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-formyl-4-methoxybenzoic acid and

Example 102b

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-5-methoxybenzene-1,2-dicarboxylic acid

Example 102A

Methyl 5-bromo-4-hydroxy-2-methoxybenzoate

To a solution of 5-bromo-2,4-dihydroxybenzoic acid monohydrate (2.76 g, 11 mmol) in methanol (5 mL) and ethyl acetate (5 mL) at 0 °C was added 2.0 N trimethylsilyl)diazomethane in hexane (6 mL). The reaction was then moved to a 40 °C water bath, and additional (trimethylsilyl)diazomethane was added slowly, until the yellow color was sustained at that temperature over 5 minutes. The solvent was then evaporated to give the title compound as a white solid (2.84 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.94 (s, 1H), 7.99 (s, 1H), 6.49 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H).

Example 102B

Methyl 5-bromo-2-methoxy-4-trifluoromethanesulfonyloxybenzoate

To a solution of the compound resulting from Example 102A (2.84 g, 10.9 mmol) in pyridine (5 mL) and dichloromethane(30 mL) at -78 °C was slowly added trifluoromethanesulfonic anhydride (2.22 mL, 13.2 mmol). After the reaction mixture was warmed to room temperature over 15 hours, it was diluted with ether (80 mL), washed with water, saturated copper(II) sulfate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 10% ethyl acetate in hexane to give the title compound (3.51 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 6.75 (s, 1 H), 3.98 (s, 3 H), 3.96 (s , 3 H).

Example 102C

Methyl 2-methoxy-4,5-divinylbenzoate

A mixture of the compound resulting from Example 102B (1.15 g, 3.0 mmol), vinyltributyltin (2.38 g, 7.5 mmol), lithium chloride (0.64 g, 15 mmol), tetrakis(triphenylphosphine)palladium(0) (0.173 g, 0.15 mmol) in nitrogen degassed anhydrous 1,4-dioxane (15 mL) was heated at 98 °C for 6 hours. The mixture was then filtered through silica gel (10 g) and then concentrated. The residue was redissolved in ether (40 mL), and water (0.2 mL) was added. To this mixture was added DBU (0.5 mL) dropwise, and the mixture was filtered through silica gel (20 g). The residue after concentration of the filtrate was purified by column chromatography eluting with hexane (200 mL) followed by 5% ethyl acetate in hexane to give the title compound (370 mg) contaminated with small amount of tributyltin derivatives. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.56 (dd, 1H), 7.01 (s, 1H), 6.98 (dd, 1H), 5.84 (dd, 1H), 5.65 (dd, 1H), 5.34 (m, 2H), 3.94 (s, 3H), 3.89 (s, 3H).

Example 102D

2-Methoxy-4,5-divinylbenzoic acid

A mixture of the compound resulting from Example 102C (370 mg) and aqueous 2 N NaOH (2 mL) in THF (6 mL) was refluxed for 7 hours. The reaction mixture was then acidified with aqueous 3 N hydrochloric acid (2 mL), diluted with ethyl acetate to 100 mL, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 10% ether in hexane followed by 100% ether to give the title compound (341 mg, 56%, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.65 (dd, 1H), 7.02 (s, 1H), 6.98 (dd, 1H), 5.84 (d, 1H), 5.66 (d, 1H), 5.48 (d, 1H), 5.44 (d , 1H), 3.97 (s, 3H).

Example 102E

N-Benzyl-N-(4-phenoxybenzyl)-2-methoxy-4,5-divinylbenzamide

To a solution of the compound resulting from Example 102D (331 mg, 1.6 mmol) in dichloromethane (5 mL) was added oxalyl chloride (2.0 M, 1.6 mL), followed by a tiny drop of DMF. After 1 hour at room temperature, the solvent was evaporated, and the residue was attached to high vacuum line (1 mm Hg) for 30 minutes. The residue was then redissolved in dichloromethane (10 mL), and to it was added N-benzyl-N-(4-phenoxybenzyl)amine (509 mg, 1.76 mmol) and 4-dimethylaminopyridine (10 mg). After 1 hour, the reaction mixture was diluted with ether (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 15% ethyl acetate in hexane to give the title compound (531 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-6.75 (m, 18H), 5.77-5.54 (m, 2H), 5.33-5.20 (m, 2H), 4.28-4.19 (m, 4H), 3.89 (2 singlets, 3H).

Example 102a

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-formyl-4-methoxybenzoic acid and

Example 102b

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-3-methoxybenzene-1,2-dicarboxylic acid

A mixture of the compound resulting from Example 102E (523 mg, 1.10 mmol), ruthenium(III) chloride monohydrate (11.4 mg, 0.055 mmol), and sodium periodate (3.53 g, 16.5 mmol) in 1:1:1.5 acetonitrile-carbon tetrachloride-water (21 mL) was stirred at room temperature for 6 hours. The reaction mixture was then filtered through celite and rinsed with ethyl acetate (100 mL). The filtrate was then washed with 0.1 N aqueous HCl (15 mL), water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 3% methanol in ethyl acetate followed by 94:5:1 ethyl acetate-methanol-formic acid to give 3-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-formyl-4-methoxybenzoic acid (102a) as the first fraction (52 mg, 9.6%), and 4-[N-benzyl-N-(4-

phenoxybenzyl)aminocarbonyl]-3-methoxybenzene-1,2-dicarboxylic acid (102b) as the second fraction (171 mg, 30%).
^{1}H NMR (500 MHz, DMSO-d_6) for benzoic acid 102a: δ 9.98 (2 singlets, 1H), 7.63 (3 singlets, 2H), 7.46-6.85 (m, 14H), 4.73 & 4.67 (2 singlets, 2H), 4.32 and 4.28 (2 singlets, 2H), 3.91 (s, 3H). MS (FAB -) m/e 494 (M-H).
^{1}H NMR (500 MHz, DMSO-d_6) for phthalic acid 102b: δ 7.55 (4 singlets, 2H), 7.42-6.85 (m, 14H), 4.25-4.05 (4 singlets, 4H), 3.88 (2 singlets, 3H). MS (FAB+) m/e, 512 (M+H), 534 (M+Na), 550 (M+K).

Example 103

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4-hydroxybenzene-1,2-dicarboxylic acid

A solution of the compound resulting from Example 102b (83 mg, 0.16 mmol), boron tribromide methyl sulfide complex (1.0 M in CH_2Cl_2, 1.6 mL) in dichloromethane (5 mL) was stirred 15 hours at room temperature. The reaction was then quenched with saturated ammonium chloride (2 mL), diluted with half saturated brine (10 mL), and extracted with 1:4 methanol-chloroform (4 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 5% methanol in ethyl acetate followed by 94:5:1 ethyl acetate-methanol-formic acid to give the title compound (53 mg, 67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67-6.87 (m, 16 H), 4.26-4.17 (4 singlets, 4 H). MS (FAB +) m/e, 498 $(M+H)^+$, 520 $(M+Na)^+$.

Example 104
2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-5-methoxy-1,4-dimethoxycarbonylbenzene

Example 104A
Methyl 4-hydroxy-2-methoxy-5-vinylbenzoate

A solution of the compound resulting from Example 102A (5.66 g, 20 mmol), vinyltributyltin (6.97 g, 22 mmol) tetrakis(triphenylphosphine)palladium (0.462 g, 0.40 mmol) in nitrogen degassed anhydrous toluene (80 mL) was heated at 108 °C for 10 hours. The mixture was then filtered through silica gel (10 g) and then concentrated. The residue was redissolved in ether (40 mL), and water (0.2 mL) was added. To this mixture was added DBU (1 mL) dropwise, and the mixture was filtered through silica gel (20 g). The residue after concentration of the filtrate was purified with column chromatography eluting with hexane (200 mL) followed by 5% ethyl acetate in hexane to give the title compound (2.62 g, 63%) contaminated with small amount of tributyltin derivatives. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (s; 1H), 7.91 (s, 1H), 6.88 (dd, 1H), 6.44 (s, 1H), 5.66 (dd, 1H), 5.19 (dd, 1H), 4.94 (s , 3H), 3.87 (s, 3H).

Example 104B
1-Carbomethoxy-2-methoxy-5-vinyl-4-trifluoromethanesulfonyloxybenzene

The procedure described in Example 102B and the compound resulting from Example 104A (2.86 g, 13.7 mmol) afforded the title compound (3.04 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.94 (dd, 1H), 6.72 (s, 1H), 5.86 (dd, 1H), 5.42 (dd, 1H), 3.95 (s, 3H), 3.92 (s, 3H).

Example 104C

1-Carbomethoxy-2-methoxy-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-4-trifluoromethanesulfonyloxybenzene

A mixture of the compound resulting from Example 104B (1.92 mg, 5.64 mmol), ruthenium(III) chloride monohydrate (60 mg, 0.28 mmol), and sodium periodate (6.03 g, 28.2 mmol) in 1:1:1.5 acetonitrile-carbon tetrachloride-water (35 mL) was stirred at 40 °C for 3 hours. The reaction mixture was then filtered through celite and rinsed with ethyl acetate (100 mL). The filtrate was then washed with 0.1 N aqueous HCl (15 mL), water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude acid was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.27 (s, 1H), 3.97 (s, 3H), 3.87 (s, 3H).

Half of the crude acid was dissolved in THF (10 mL), and to it was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (704 mg, 3.67 mmol), N-benzyl-N-(4-phenoxybenzyl)amine (897 mg, 3.10 mmol), and 4-dimethylaminopyridine (50 mg). After 6 hours at room temperature, the reaction mixture was diluted with ether (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 20% ethyl acetate in hexane to give the title compound (0.887 g, 50%, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (2 singlets, 1H), 7.40-6.76 (m, 15H), (2 br. multiplets, 2H), 4.23 & 4.18 (2 singlets, 2H), 3.98-3.67 (4 singlets, 6H).

Example 104D

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-5-methoxy-1,4-dimethoxycarbonylbenzene

A carbon monoxide degassed mixture of the compound resulting from Example 104C (867 mg, 1.38 mmol), palladium(II) acetate (16 mg, 0.07 mmol), 1,3-bis(diphenylphosphino)propane (29 mg, 0.07 mmol) and triethylamine (281 mg, 2.76 mmol) in methanol (2 mL) and DMF (5 mL) was heated to 65 °C under a carbon monoxide balloon for 15 hours. The reaction mixture was diluted with 1:1 ether-ethyl acetate (100 mL), washed with 10% aqueous HCl, water, and brine, dried over anhydrous magnesium sulfate, filtered, and

concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (631 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (2 singlets, 1H), 7.40-6.92 (m, 15H), 4.90 and 4.50 (2 br. multiplets, 2H), 4.22 and 4.18 (2 singlets, 2H), 3.98-3.67 (5 singlets, 9H). MS (DCI) m/e, 540 $(M+H)^+$.

Example 105

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-5-methoxybenzene-1,4-dicarboxylic acid

The procedure described in Example 98E and the compound resulting from Example 104 (574 mg, 1.06 mmol) afforded the title compound (517 mg, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (2 singlets, 1H), 7.63 (2 singlets, 1H), 7.43-6.90 (14H), 4.92-4.78 and 4.45-4.15 (m, 4H), 3.92 and 3.90 (2 singlets, 3H). MS (FAB-) m/e 510 (M-H).

Example 106

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-5-hydroxybenzene-1,4-dicarboxylic acid

A solution of the compound resulting from Example 105 (200 mg, 0.39 mmol), boron tribromide methyl sulfide complex (1.16 g, 3.7 mmol) in anhydrous 1,2-dichloroethane was refluxed for 50 hours. The reaction was then quenched with saturated sodium bicarbonate, diluted with ethyl acetate (100 mL), washed with 10% aqueous HCl, water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 94:5:1 ethyl acetate-methanol-formic acid to give the title compound (135 mg, 70%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (br. s, 1H), 9.5 (m, 1H), 8.54 (br. s, 1H), 7.80 (br. s, 1H), 7.42-6.88 (m,14H), 4.65-4.50 and 4.30 (6 br. singlets, 4H). MS (FAB -) m/e 496 (M-H).

Example 107
4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-methoxy-1,3-dimethoxycarbonylbenzene

Example 107A
Dimethyl 4-triflyloxy-6-methoxy-1,3-isophthalate

A mixture of the compound resulting from Example 104B (1.10 g, 3.23 mmol), ruthenium chloride monohydrate (32 mg, 0.16 mmol), and sodium periodate (3.51 g, 16.2 mmol) in 1:1:1.5 acetonitrile-carbon tetrachloride-water (28 mL) was stirred at 45 °C for 6 hours. The reaction mixture was then filtered through celite and rinsed with ethyl acetate (100 mL). The filtrate was then washed with 0.1 N aqueous HCl (15 mL), water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in 3:1 ethyl acetate-methanol (10 mL), cooled in a 0 °C water bath, and treated with (trimethylsilyl)diazomethane (2.0 M in hexane) in small portions until the yellow color persisted. The solvent was evaporated, and the residue was purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (915 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 6.83 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H).

Example 107B
Dimethyl 6-methoxy-4-vinyl-1,3-isophthalate

The procedure described in Example 102C, the compound resulting from Example 107A (905 mg, 2.43 mmol) and tributylvinyltin (849 mg, 2.68 mmol) afforded the title compound (114 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.60 (dd, 1H), 7.10 (s, 1H), 5.71 (d, 1H), 5.47 (d, 1H), 4.01 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H).

Example 107C

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-methoxy-1,3-dimethoxycarbonylbenzene

A mixture of the compound resulting from Example 107B (103 mg, 0.412 mmol), ruthenium(III) chloride monohydrate (5 mg), and sodium periodate (0.5 g) in 1:1:1.5 acetonitrile-carbon tetrachloride-water (7 mL) was stirred at 60 °C for 6 hours. The reaction mixture was then filtered through celite and rinsed with ethyl acetate (50 mL). The filtrate was then washed with 0.1 N aqueous HCl (5 mL) and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude dimethyl 4-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-methoxy-1,3-isophthalate was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.35 (s, 1 H), 3.97 (s , 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H).

The crude acid from above was reacted by the procedures described in Example 102E to give the title compound (217 mg, 98%, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (2 singlets, 1H), 7.50-6.84 (m, 15H), 4.25 and 4.19 (2 br. singlets, 4H), 3.90-3.74 (6 singlets, 9H). MS (DCI) m/e 540 $(M+H)^+$.

Example 108

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-methoxy-benzene-1,3-dicarboxylic acid

The procedure described in Example 98E and the compound resulting from Example 107C (143 mg, 0.26 mmol) afforded the title compound (32 mg, 24%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.0 (br. s, 1H), 7.77 (br. s, 1H), 7.43-6.90 (m, 14H), 4.83-4.15 (m, 4H), 3.91 and 3.89 (2 singlets, 3H). MS (FAB -) m/e 510 (M-H).

Example 109

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-hydroxy-benzene-1,3-dicarboxylic acid

The procedure described in Example 106 and the compound resulting from Example 107 (162 mg, 0.30 mmol) afforded the title compound (79 mg, 53%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.03 (br. s, 1H), 11.09 (2 singlets, 1H), 9.52 (m, 1H), 8.38 (2 singlets, 1H), 7.43-6.82 (m, 15H), 4.95-4.15 (m, 4H). MS (FAB-) m/e (M-H), 496.

Example 110

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,3-dimethoxycarbonylbenzene

Example 110A

3,5-Dimethoxycarbonylbenzoic acid

To a stirred solution of 1,3,5-trimethoxycarbonylbenzene (2.52 g, 10 mmol., 1.0 eq.) in 40 mL of 3:1 methanol-THF at ambient temperature was added a solution of 0.64 g (10 mmol, 1.0 eq.) of KOH in 6 mL of methanol, and the resulting solution was stirred overnight. The slurry formed was then concentrated and partioned between ethyl ether and water. The aqueous phase was extracted with an additional portion of ethyl ether and then acidified with concentrated aqueous HCl. The resulting suspension was extracted with 2 portions of ethyl acetate, and the combined organic phases were washed with water and brine, dried, filtered and concentrated to give a white solid that was used without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76-8.84 (m, 3H), 3.97 (s, 6H). MS (DCI, NH_3): 273 (35%); 256 (100%); 212 (10%).

Example 110B

3,5-Bis(methoxycarbonyl)benzoyl chloride

To a stirred suspension of 476 mg (2 mmol, 1 eq.) of the compound resulting from Example 110A in 20 mL of CH_2Cl_2 at room temperature was added 0.21 mL (2.4 mmol, 1.2 eq.) of oxalyl chloride dropwise *via* syringe. After the addition was complete, 2 drops of dry DMF were added and the mixture stirred for 1.5 hours. To the yellow solution was added 5 mL of toluene, and the mixture was concentrated to give 510 mg (99%) of the title compound as an off white solid that was used without further purification.

Example 110C

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-1,3-dimethoxycarbonylbenzene

To a stirred solution of 342 mg (1.05 mmol, 1.05 eq.) of N-benzyl-N-(4-phenoxybenzyl)amine-HCl in 5 mL of CH_2Cl_2 was added 0.31 mL (2.2 mmol, 2.2 eq.) of triethylamine. To the resulting solution was added 256 mg (1.0 mmol, 1.0 eq.) of the compound resulting from Example 110B dissolved in 5 mL of CH_2Cl_2 dropwise, and stirring was continued for 2 hours at room temperature. The mixture was poured into 50 mL of hexanes and extracted with 2 portions of water, 2 portions of 3 N aqueous HCl, 1 portion of brine and then dried, filtered and concentrated. The residue was purified by column chormatography on SiO_2 (25 g) eluting with 15-25% ethyl acetate in hexanes to give 326 mg (64%) of the title compound as a thick syrup. ^1H NMR (300 MHz., $CDCl_3$) δ 8.70 (t, 1H), 8.33 (d, 2H), 7.36 (m, 7H), 7.13 (m, 2H), 7.01 (m, 5H), 4.54 (broad AB quartet, 4H), 3.92 (s, 6H). MS (DCI, NH_3) m/e 527 (100%); 510 (78%). HRMS (FAB+) calcd for $C_{31}H_{28}NO_6$ (M+H) 510.1917. Found: 510.1903. Anal calcd for $C_{31}H_{27}NO_6 \cdot 0.19\ H_2O$: C, 73.07; H, 5.34; N, 2.75. Found: C, 72.58; H,5.26; N, 2.62.

Example 111

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-3-methoxycarbonylbenzoic acid

To a stirred solution of 347 mg (0.68 mmol, 1.0 eq.) of the compound resulting from Example 110 in 9 mL of THF at -10 °C was added a solution of 29 mg (0.68 mmol, 1.0 eq.) of LiOH in 3 mL of H_2O. Methanol was added until a clear solution was obtained. The bath was replaced after 1 hour with an ice water bath and the mixture allowed to stir overnight during which time the ice bath melted. The mixture was quenched with excess aqueous HCl and poured into 3 N aqueous HCl. The suspension was extracted with 2 portions of ethyl acetate, and the combined organic phases were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 98:1.5:0.5 going to 90:10:1 $CHCl_3$-methanol-acetic acid to give 93 mg (27%) recovered diester and 185 mg (55%) of the title compound as a white foam. ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (t, 1H), 8.37 (d, 2H), 7.34 (m, 7H), 7.11 (m, 2H), 7.01 (m, 5H), 4.53 (broad AB quartet, 4H), 3.92 (s, 3H). MS (DCI NH_3): 513 (50%); 496 (55%); 404, (10%); 273 (18%); 256 (78%); 241 (100%); 200 (60%); 183 (83%). Anal calcd for $C_{30}H_{25}NO_6 \cdot 0.36$ H_2O: C, 72.72; H, 5.08; N, 2.83. Found: C, 71.78; H, 5.17; N, 3.20.

Example 112

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]benzene-1,3-dicarboxylic acid

To a stirred solution of 322 mg (0.63 mmol, 1.0 eq.) of the compound resulting from Example 111 in 9 mL of THF was added a solution of 79 mg (1.90 mmol, 3 eq.) of LiOH in 3 mL of H_2O, and the solution was stirred overnight. The basic mixture was quenched with 3 N aqueous HCl and partioned between 3 N aqueous HCl and 2 portions of ethyl acetate. The combined organic phases were washed with brine, dried, filtered and concentrated. The residue was lyophilized to give 282 mg (91%) of the title compound as a fluffy white solid. ^1H NMR (300 MHz., CD_3OD) δ 8.68 (t, 1H), 8.24 (t, 2H), 7.34 (m, 7H), 7.12 (m, 2H), 6.97 (m, 5H), 4.47 (m, 2H), 2 protons buried under MeOH peak. MS (FAB+): 482 (60%); 460 (18%); 307 (23%); 289

(18%); 183 (15%); 154 (100%); 136 (70%). Anal calcd for $C_{29}H_{23}NO_6 \cdot 0.98$ H_2O: C, 72.34; H, 4.81; N, 2.91. Found: C, 69.78; H, 4.99; N, 2.69.

Example 113

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-3-carboxamidobenzoic acid

Example 113A

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-3-(N-benzyloxyamino)carbonylbenzoic acid methyl ester

To a stirred solution of the compound resulting from Example 112 (50 mg, 0.10 mmol, 1.0 eq.) in 1 mL of THF at -10 °C was sequentially added 12 µL (0.11 mmol, 1.1 eq.) of 4-methylmorpholine and 14 µL (0.11 mmol, 1.1 eq.) of isobutylchloroformate and stirring was continued for 30 minutes. To the resulting white suspension was added 19 mg (0.12 mmol, 1.2 eq.) of O-benzylhydroxylamine hydrochloride followed by 13 µL of N-methylmorpholine and stirring was continued overnight . The reaction mixture was partitioned between ethyl acetate and H_2O. The aqueous phase was extracted with an additional portion of ethyl acetate and the combined organic phases were washed with 3 N aqueous HCL and brine, dried, filtered and concentrated. Column chromatography on SiO_2 (15 g) eluting with 40% ethyl acetate in hexanes gave 45 mg (75%) of the title compound as a thick syrup. ^1H NMR (300 MHz., $CDCl_3$) δ 8.31 (s, 1H), 8.24 (s, 1H), 7.93 (bd, 1H), 7.25-7.46 (m, 12H), 6.93-7.17 (m, 7H), 5.02 (bs, 2H), 4.51 (broad AB quartet, 4H), 3.92 (s, 3H). MS (DCI, NH_3): 618 (100%); 601 (100%); 512 (62%); 495 (30%); 361 (47%); 255 (38%); 213 (77%).

Example 113B

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-3-carboxamidobenzoic acid

To a stirred solution of 42 mg (0.07 mmol, 1.0 eq.) of the compound resulting from Example 113A in 0.75 mL of THF was added a solution of 6 mg (0.14 mmol 2.0 eq.) of $LiOH-H_2O$ in 0.25 mL of H_2O. The mixture was stirred overnight and quenched by the addition of 3 N aqueous HCl and poured into a separatory funnel containing 3 N aqueous HCl and ethyl acetate. The layers

were separated and the aqueous layer was extracted with 2 additional portions of ethyl acetate. The combined organic phases were washed with brine, dried, filtered and concentrated. The residue was dissolved in 3 mL of ethanol and the solution purged with N_2. To this solution was added 40 mg of 10% Pd/C and the suspension stirred under a balloon of H_2 for 20 hours. The mixture was filtered through a pad of celite, washed with ethanol and concentrated to give 23 mg of the title compound as a white foam. ^{1}H NMR (300 MHz., DMSO-d_6) δ 8.48 (s, 1H), 8.24 (s, 1H), 8.13 (s, 1H), 8.02 (s, 1H), 7.51 (s, 1H), 7.34 (m, 7H), 7.12 (m, 2H), 6.98 (m, 5H), 4.66 (bd, 2H), 4.43 (bs, 2H). MS (DCI NH_3) m/e 498 (100%); 481 (40%). MS (FAB+): 503 (M+Na$^+$, 18%); 481 (M+H$^+$, 80%); 460 (45%); 307 (25%); 154 (100%); 136 (63%). MS (FAB-): 479 (M-H, 60%); 459 (42%); 306 (38%); 199 (30%); 168 (40%); 153 (100%); 122 (18%). Anal calcd for $C_{29}H_{24}N_2O_5 \cdot 1.54\ H_2O$: C, 72.49; H, 5.03; N, 5.83. Found: C, 68.54; H, 5.02; N, 5.20.

Example 114

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-hydroxymethylbenzoic acid

Example 114A

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-hydroxymethylbenzoic acid methyl ester

To a stirred solution of 495 mg (1.0 mmol. 1.0 eq.) of the compound resulting from Example 111 in 5 mL of THF at 0 °C was added 0.12 mL (1.1 mmol, 1.1 eq.) of N-methylmorpholine. After 30 minutes of stirring, 0.14 mL (1.05 mmol, 1.05 eq.) of isobutylchloroformate was added dropwise and stirring was continued for an additional 30 minutes. To this suspension was added 227 mg (6.0 mmol, 6.0 eq.) of $NaBH_4$ followed immediately by the addition of 1 mL of saturated aqueous $NaHCO_3$ solution, and the mixture was stirred for 1 hour more and quenched by the addition of 0.5 M H_3PO_4. The reaction mixture was partitioned between ethyl acetate (2 x 20 mL) and 0.5 M aqueous H_3PO_4 (10 mL). The combined organic phases were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 1:1 ethyl acetate-hexanes to give 409 mg (85%) of the

title compound as a white foam contaminated with a small amount of an unknown impurity. ^{1}H NMR (300 MHz. $CDCl_3$) δ 8.06 (s, 2H), 7.18 (s, 1H), 7.37 (m, 7H), 7.13 (m, 2H), 7.02 (m, 5H), 4.74 (m, 4H), 4.39 (d, 2H), 3.91 (s, 3H). MS (DCI, NH_3) m/e 482 (100%).

Example 114B

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-hydroxymethylbenzoic acid

To a stirred solution of the compound resulting from Example 114A (32 mg, 0.066 mmol, 1.0 eq.) in 1.5 mL of THF was added a solution of 6 mg (0.14 mmol, 2.0 eq.) of LiOH-H_2O in 0.5 mL of H_2O and stirring was continued overnight. The mixture was quenched by the addition of 3 N aqueous HCl and partitioned between ethyl acetate and 3 N aqueous HCl. The aqueous phase was extracted with an additional portion of ethyl acetate, and the combined organic phases were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (15 g) eluting with 97:2:1 going to 94:5:1 $CHCl_3$-methanol-acetic acid and subsequently lyophilized to give 30 mg (97%) of the title compound as a fluffy lyophilate. ^{1}H NMR (300 MHz. $CDCl_3$) δ 8.06 (s, 1H), 8.05 (s, 1H), 7.65 (s, 1H), 7.34 (m, 7H), 7.12 (m, 2H), 7.01 (m, 5H), 4.71 (m, 4H), 4.36 (d, 2H). MS (DCI, NH_3) m/e 485 (63%); 468 (100%). HRMS (FAB^+): calcd for $C_{29}H_{26}NO_5$ (MH^+): 468.1811. Found: 468.1808.

Example 115

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-formylbenzoic acid

Example 115A

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-formylbenzoic acid methyl ester

To a stirred solution of the 151 mg (0.31 mmol, 1.0 eq.) of the compound resulting from Example 114 in 5 mL of 10% acetonitrile in CH_2Cl_2 was added 54 mg (0.46 mmol, 1.6 eq.) of N-methylmorpholine followed by 300 mg of active 4Å molecular sieves, and stirring was continued for 15 minutes. To this suspension was added 6 mg (0.016 mmol, 0.05 eq.) of TPAP and the mixture

stirred for an additional 45 minutes during which time it turned from green to black. To the suspension was added celite (~1 g) and 15 mL of ethyl ether, and vigorous stirring was continued for 2 minutes, and then the suspension was filtered through a 1/2" X 1" pad of SiO_2 (prewetted with ether) and washed generously with ether. The filtrate was concentrated and the residue purified by column chromatography on SiO_2 (20 g) eluting with 35% ethyl acetate in hexanes to give 103 mg (69%) of the title compound as a white foam. ^1H NMR (300 MHz., $CDCl_3$) δ 10.04 (s, 1H), 8.55 (t, 1H), 8.39 (t, 1H), 8.17 (t, 1H), 7.37 (m, 7H), 7.11 (m, 2H), 7.02 (m, 5H), 4.72 (bd, 2H), 4.38 (bd, 2H), 3.95 (s, 3H). MS (DCI, NH_3) m/e 497 (98%); 480 (100%).

Example 115B

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-formylbenzoic acid

Using the procedure of Example 114B and the compound resulting from Example 115A, the title compound was prepared. ^1H NMR (300 MHz., $CDCl_3$) δ 10.04 (s, 1H), 8.61 (s, 1H), 8.44 (t, 1H), 8.21 (s, 1H), 7.38 (m, 7H), 7.13 (m, 2H), 7.02 (m, 5H), 4.74 (d, 2H), 4.40 (d, 2H). MS (DCI, NH_3) m/e 483 (75%); 466 (100%). HRMS (FAB^+): calcd for $C_{29}H_{24}NO_5$: 466.1654. Found: 466.1655.

Example 116

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(N-hydroxyiminoformyl)benzoic acid

Example 116A

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(N-hydroxyiminoformyl)benzoic acid methyl ester

To a stirred solution of 200 mg (0.42 mmol, 1.0 eq.) of the compound resulting from Example 115A in 4 mL of methanol was sequentially added 41 mg (0.50 mmol, 1.2 eq.) of sodium acetate and 35 mg (0.50 mmol, 1.2 eq.) of hydroxylamine hydrochloride. After stirring for an additional hour, the mixture was partitioned between ethyl acetate and H_2O. The organic phase was dried, filtered and concentrated to give 200 mg (99%) of the title compound as a white

foam. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.23 (t, 1H), 8.12 (t, 1H), 7.94 (t, 1H), 7.63 (s, 1H), 7.36 (m, 7H), 7.13 (m, 2H), 7.01 (m, 5H), 4.72 (m, 2H), 4.39 (m, 2H), 3.92 (s, 3H). MS (DCI, NH_3) m/e 495 (60%); 213 (100%).

Example 116B

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(N-hydroxyiminoformyl)benzoic acid

To a stirred solution of 30 mg (0.058 mmol, 1.0 eq.) of the compound resulting from Example 116A in 1 mL of methanol was added 0.1 mL (0.4 mmol, 6.5 eq.) of 4 N aqueous NaOH solution and stirring was continued for 2 hours. The reaction was quenched by the addition of 1 mL of 3 N aqueous HCl and poured into water and extracted 2x with ethyl acetate. The combined organic phases were washed with brine, dried, filtered and concentrated to give 29 mg (103%) of the title compound as a white foam. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.28 (t, 1H), 8.20 (t, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.31 (m, 7H), 7.13 (m, 2H), 7.02 (m, 5H), 4.72 (bd, 2H), 4.40 (bd, 2H). MS (DCI, NH_3) m/e 498 (42%); 481 (100%). Anal calcd for $C_{29}H_{24}N_2O_5 \cdot 0.56\ H_2O$: C, 72.49; H, 5.03; N, 5.83. Found: C, 71.00; H, 5.35; N, 5.55.

Example 117

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(1*H*-tetrazolyl)benzoic acid methyl ester

Example 117A

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-cyanobenzoic acid methyl ester

To a stirred solution of 171 mg (0.33 mmol, 1.0 eq.) of the compound resulting from Example 116A in 3 mL of acetonitrile at -10 °C were sequentially added 0.14 mL (0.99 mmol, 3.0 eq.) of triethylamine and 29 µL (0.37 mmol, 1.1 eq.) of methanesulfonyl chloride. The cold bath was removed and the mixture stirred for 2 hours. The yellow mixture was partitioned between H_2O and ethyl acetate. The combined organic extracts were dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (20 g) eluting

with 20% ethyl acetate in hexanes to give 123 mg (76 %) of the title compound. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.34 (m, 2H), 7.90 (s, 1H), 7.38 (m, 7H), 7.13 (m, 2H), 7.02 (m, 5H), 4.72 (bd, 2H), 4.36 (bd, 2H), 3.95 (s, 3H). MS (DCI, NH_3) m/e 494 (100%); 477 (85%); 217 (40%); 200 75%); 183 (93%).

Example 117B

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(1*H*-tetrazolyl)benzoic acid methyl ester

A mixture of 120 mg (0.25 mmol, 1.0 eq.) of the compound resulting from Example 117A, 98 mg (1.50 mmol, 6.0 eq.) of NaN_3 and 206 mg (1.50 mmol, 6.0 eq.) of Et_3N-HCl in 3 mL of DMF was heated in an oil bath at 100 °C for 3 hours. The cooled reaction mixture was partitioned between 3 N aqueous HCl and ethyl acetate. The aqueous phase was extracted with 2 additional portions of ethyl acetate, and the combined organics were washed with 3 portions of water and 1 portion of brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (20 g) eluting with 97:2:1 $CHCl_3$-methanol-acetic acid to give 128 mg (98%) of the title compound as thick oil. A portion of this material was lyophilized for analysis. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.77 (s, 1H), 8.44 (s, 1H), 8.18 (s, 1H), 7.36 (m, 7H), 7.15 (m, 2H), 7.04 (m, 5H), 4.83 (bd, 2H), 4.51 (bd, 2H), 3.90 (2s (due to isomeric tetrazoles), 3H). MS (DCI, NH_3) m/e 520 (95%); 183 (100%). Anal calcd for $C_{30}H_{25}N_5O_4 \cdot 0.61\ H_2O$: C, 69.35; H, 4.85; N, 13.48. Found: C, 67.92; H, 4.93; N, 13.21.

Example 118

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(1*H*-tetrazolyl)benzoic acid

Using the procedures of Example 116B and the compound resulting from Example 117B, the title compound was prepared. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.65 (s, 1H), 8.44 (s, 1H), 8.21 (s, 1H), 7.32 (m, 7H), 7.09 (m, 2H), 6.98 (m, 5H), 4.80 (bd, 2H), 4.46 (bd, 2H). MS (DCI, NH_3) m/e 523 (10%); 506 (100%); 415 (20%); 366 (15%). Anal calcd for $C_{29}H_{23}N_5O_4 \cdot 0.75\ H_2O$: C, 68.90; H, 4.85; N, 13.85. Found: C, 67.19; H, 4.91; N, 13.16.

Example 119

3-[N-Benzyl-N-4-phenoxybenzylaminocarbonyl]-5-(N-hydroxyaminocarbonyl)benzoic acid

To a stirred solution of 99 mg (0.2 mmol, 1.0 eq.) of the compound resulting from Example 114A in 2 mL of CH_2Cl_2 at 0 °C were sequentially added 46 µL (0.42 mmol, 2.10 eq.) of N-methylmorpholine and 27 µL (0.21 mmol, 1.05 eq.) of isobutylchloroformate, and the solution was stirred for 30 minutes. To the reaction mixture was added 32 mg (0.22 mmol, 1.1 eq.) of O-tert-butyldimethylsilyl-hydroxylamine-HCl and stirring was continued for 2 hours. The reaction mixture was concentrated, the residue was dissolved in 2 mL of THF, and 1 mL of 1 N aqueous HCl was added. The mixture was stirred overnight and partitioned between ethyl acetate (3x) and water. The combined organic phases were washed with brine, dried, filtered and concentrated. The crude residue was dissolved in 2 mL of 1:1 THF methanol, 0.5 mL of 4 N aqueous NaOH solution was added, and the mixture was stirred overnight. The reaction mixture was acidified with excess 3 N aqueous HCl and poured into a separatory funnel containing water and ethyl acetate. The aqueous phase was extracted with 2 additional portions of ethyl acetate, and the combined organic phases were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (15 g) eluting with 94:5:1 $CHCl_3$-methanol-acetic acid to give 37 mg (37%) of the title compound as a white foam. Lyophilization gave a white powder. ^1H NMR (300 MHz., DMSO-d_6) δ 8.36 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.35 (m, 7H), 7.13 (m, 3H), 6.99 (m, 4H), 4.62 (bd, 2H), 4.44 (bd, 2H). MS (DCI, NH_3) m/e 497 (100%); 453 (18%); 183 (45%); 117 (22%); 111 (31%). Anal calcd for $C_{29}H_{24}N_2O_6 \cdot 1.18\ H_2O$: C, 70.15; H, 4.87; N, 5.64. Found: C, 67.27; H, 4.90; N, 5.14.

Example 120
5-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]benzene-1,3-dicarboxylic acid

Example 120A
5-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]-1,3-dimethoxycarbonylbenzene

To a stirred solution of the compound resulting from Example 110A (238 mg, 1.0 mmol, 1.0 eq.) in 10 mL of dry dioxane was added 0.24 mL (2.2 mmol, 2.2 eq.) of N-methylmorpholine followed by 0.24 mL (1.1 mmol, 1.1 eq.) of diphenylphosphoryl azide, and stirring was continued for 1 hour. The resulting solution was heated to 80 °C for 1 hour and then allowed to cool to room temperature. To the yellow/brown solution was added 358 mg (1.1 mmol, 1.1 eq.) of N-benzyl-N-(4-phenoxybenzyl)amine-HCl and the suspension stirred at room temperature for 12 hours and at reflux for 4 hours. The cooled reaction mixture was concentrated and the residue purified by column chromatography on SiO_2 (25 g) eluting with 30% ethyl acetate in hexanes to give 299 mg (57%) of the title compound as a white foam. ^1H NMR (300 MHz., $CDCl_3$) δ 8.32 (t, 1H), 8.12 (s, 1H), 8.11 (s, 1H), 7.33 (m, 9H), 7.12 (m, 1H), 7.03 (m, 4H), 6.53 (s, 1H), 4.62 (s, 4H), 3.90 (s, 3H). MS (DCI, NH_3) m/e 542 (10%); 290 (100%); 270 (12%).

Example 120B
5-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]benzene-1,3-dicarboxylic acid

Using the procedure described in Example 112 and the compound resulting from Example 120A, the title compound was prepared. ^1H NMR (300 MHz., CD_3OD) δ 8.32 (m, 1H), 8.30 (m, 2H), 7.31 (m, 9H), 7.09 (m, 1H), 6.96 (m, 4H), 4.64 (s, 2H), 4.60 (s, 2H). MS (FAB+) m/e 497 (62%); 405 (30%); 289 (18%); 183 (28%); 154 (100%); 136 (85%); 107 (30%). MS (FAB-): 495 (M-H, 70%); 459 (18%); 306 (30%); 199 (28%); 168 (28%); 153 (100%). HRMS: calcd for $C_{29}H_{25}N_2O_6$: 497.1713. Found: 497.1708.

Example 121a

5-[N-Benzyl-N-4-phenoxybenzylaminosulfonyl]-3-methoxycarbonylbenzoic acid and

Example 121b

5-[N-Benzyl-N-4-phenoxybenzylaminosulfonyl]benzene-1,3-dicarboxylic acid

Example 121A

3,5-Bis(methoxycarbonyl)benzenesulfonyl chloride

To a stirred suspension of 548 mg (2 mmol, 1 eq.) of 3,5-bis(methoxycarbonyl)-benzenesulfonic acid in 10 mL of 1,2-dichloroethane was added 0.30 mL (4 mmol, 4 eq.) of thionyl chloride and 2 drops of DMF. The mixture was then heated to reflux for 20 hours whereupon an additional 0.30 mL (4 mmol, 4 eq.) of thionyl chloride was added. After 3 more hours at reflux, the suspension was filtered while hot and concentrated to give 311 mg (53%) of the title compound as a white solid. ^{1}H NMR (300 MHz., $CDCl_3$) δ 9.02 (m, 1H), 8.86 (m, 2H), 4.03 (s, 6H). MS (DCI, NH_3) m/e 327 (40%); 310 (100%); 212 (70%).

Example 121B

3,5-Bis(methoxycarbonyl)-1-[N-benzyl-N-(4-phenoxybenzyl)]benzenesulfonamide

To a stirred suspension of 358 mg (1.1 mmol, 1.1 eq.) of N-benzyl-N-(4-phenoxybenzyl)amine-HCl in 5 mL of CH_2Cl_2 at 0 °C was added 0.42 mL 2.4 mmol, 2.4 eq.) of Hunigs base. After stirring the mixture for 5 minutes, a solution of the compound resulting from Example 121A (292 mg, 1.0 mmol, 1.0 eq.) in 5 mL of CH_2Cl_2 was added dropwise, the solution was stirred 20 minutes at 0 °C and overnight at room temperature and concentrated to dryness. The residue was purified by careful column chrmoatography on SiO_2 (25 g) eluting with 25% ethyl acetate in hexanes to give 321 mg (59%) of the title compound as a white foam. ^{1}H NMR (300 MHz., $CDCl_3$) δ 8.84 (m, 1H), 8.58 (m, 2H), 7.34 (m, 2H), 7.23 (m, 3H), 7.14 (m, 3H), 7.06 (m, 2H), 6.95 (m, 2H), 6.86 (m, 2H), 4.42 (s, 2H), 4.37 (s, 2H), 3.99 (s, 6H). MS (DCI, NH_3) m/e 563 (40%); 288 (30%); 217 (47%); 200 (100%).

Example 121a

5-[N-Benzyl-N-4-phenoxybenzylaminosulfonyl]-3-methoxycarbonylbenzoic acid and

Example 121b

5-[N-Benzyl-N-4-phenoxybenzylaminosulfonyl]benzene-1,3-dicarboxylic acid

To a solution of 310 mg (0.57 mmol, 1.0 eq.) of the compound resulting from Example 121B in 7.5 mL of THF at 0 °C was added a solution of 36 mg (0.85 mmol, 1.5 eq.) of LiOH-H_2O in 2.5 mL of H_2O. Methanol was added to obtain a homogeneous solution and the mixture was stirred for 2 hours and quenched by the addition of 3 N aqueous HCl. The quenched mixture was partitioned between ethyl acetate (2x) and 3 N aqueous HCl. The combined organic phases were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 98:1.5:0.5 $CHCl_3$-methanol-acetic acid to give 151 mg (50%) the monester 121a as a white foam. ^1H NMR (300 MHz., DMSO-d_6) δ 8.62 (t, 1H), 8.41 (t, 1H), 8.34 (t, 1H), 7.38 (m, 2H), 7.23 (m, 3H), 7.15 (m, 5H), 6.88 (m, 2H), 6.82 (m, 2H), 4.44 (s, 2H), 4.39 (s, 2H), 3.93 (s, 3H). MS (FAB$^+$) m/e 531 (70%); 183 (60%); 154 (100%); 136 (70%). MS (FAB$^-$): 530 (95%); 306 (59%); 305 (58%); 168 (40%); 153 (100%); 122 (18%). Anal calcd for $C_{29}H_{25}NO_7S$: C, 65.53; H, 4.74; N, 2.63. Found: C, 65.78; H, 4.82; N, 2.60. Furth

Further elution with 94:5:1 $CHCl_3$-methanol-acetic acid gave 123 mg (42%) of the diacid 121b as a white solid. ^1H NMR (300 MHz., DMSO-d_6) δ 8.63 (t, 1H), 8.39 (m, 2H), 7.38 (m, 2H), 7.24 (m, 3H), 7.16 (m, 5H), 6.88 (m, 2H), 6.81 (m, 2H), 4.43 (s, 2H), 4.38 (s, 2H). MS (FAB$^+$) m/e 540 (15%); 517 (M+, 40%); 307 (20%); 183 (45%); 154 (100%); 136 (75%); 107 (25%). MS (FAB.): 516 (84%); 30650%); 305 (48%); 246 (17%); 199 (36%); 168 (39%); 153 (100%); 122 (18%). Anal calcd for $C_{28}H_{23}NO_7S$: C, 64.98; H, 4.48; N, 2.71. Found: C, 74.79; H, 4.65; N, 2.52.

Example 122
4-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]-2-carboxymethoxybenzoic acid

Example 122A
4-t-Butoxycarbonylaminosalicylic acid

To a stirred suspension of 3.82 g (25 mmol, 1 eq.) of 4-aminosalicylic acid in 100 mL of 3:1 THF-H_2O was added 10.36 g (75 mmol, 3 eq.) of K_2CO_3 in 50 mL of H_2O. After stirring for an additional 10 minutes, a solution of 6.54 g (30 mmol, 1.2 eq.) of di-t-butyl-dicarbonate in 50 mL of THF was added and the biphasic mixture stirred vigorously for 72 hours. The mixture was concentrated to remove the THF, and the aqueous phase was carefully acidified with 3 N aqueous HCl. This mixture was then extracted with 3 portions of ethyl acetate and the combined organic phases were washed with brine, dried, filtered, and concentrated. The resulting brown solid was recrystallized from toluene/ethyl acetate to give 3.54 g of the title compound as a light brown solid. ^1H NMR (300 MHz., $CDCl_3$) δ 10.53 (s, 1H), 8.82 (d, 1H), 7.07 (d, 1H), 6.92 (dd, 1H), 6.71 (bs, 1H), 1.54 (s, 9H). MS (DCI, NH_3) m/e 271 (100%); 236 (10%); 215 (20%); 136 (38%).

Example 122B
4-t-Butoxycarbonylaminosalicylic acid methyl ester

To a stirred solution of 1.68 g (6.63 mmol) of the compound resulting from Example 122A in 20 mL of 10% methanol in ether at 0 °C was added excess trimethylsilyl-CH_2N_2. (TMS CH_2N_2) The yellow solution was stirred at 0 °C for 30 minutes and at room temperature for 30 minutes and the excess $TMSCH_2N_2$ was quenched by the addition of excess acetic acid. The solution was concentrated and the residue recystallized from hexanes to give 1.31 g (75%) of the title compound as a white solid. ^1H NMR (300 MHz. $CDCl_3$) δ 10.84 (s, 1H), 7.74 (d, 1H), 6.98 (d, 1H), 6.93 (dd, 1H), 6.57 (bs, 1H), 3.92 (s, 3H), 1.53 (s, 9H). MS (DCI, NH_3) m/e 285 (100%); 268 (18%); 229, (30%).

Example 122C

4-(t-Butoxycarbonylamino)-2-methoxycarbonylmethoxybenzoic acid methyl ester

To a stirred solution of 267 mg (1.0 mmol, 1.0 eq.) of the compound resulting from Example 122B in 2 mL of DMF at room temperature were sequentially added 0.11 mL (1.2 mmol, 1.2 eq.) of methyl bromoacetate and 152 mg (1.1 mmol, 1.1 eq.) of K_2CO_3, and the suspension was vigorously stirred for 12 hours. The mixture was partitioned between water and ethyl acetate (2x). The combined organic phases were washed with 2 portions of water and 1 portion of brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 30% to 50% ethyl acetate in hexanes to give the title compound as a thick oil. ^1H NMR (300 MHz., $CDCl_3$) δ 7.83 (d, 1H), 7.27 (d. 1H), 6.83 (dd, 1H), 6.64 (bs, 1H), 4.74 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 1.5,(s, 9H). MS (DCI, NH_3) m/e 357 (100%); 340 (55%); 283 (15%).

Example 122D

4-Amino-2-methoxycarbonylmethoxybenzoic acid methyl ester

The compound resulting from Example 122C (250 mg) was dissolved in 2 mL of 4 N HCL in dioxane and stirred for 8 hours. The resulting solution was concentrated to dryness to give 177 mg (100%) of the title compound as a thick oil. ^1H NMR (300 MHz., $CDCl_3$) δ 7.74 (bd, 1H), 7.09 (m, 2H), 4.72 (s, 2H), 3.88 (s, 3H), 3.71 (s, 3H). MS (DCI, NH_3) m/e 257 (100%); 240 (80%).

Example 122E

N-Benzyl-N-(4-phenoxybenzyl)-carbamoyl chloride

To a suspension of 3.26 g (10 mmol, 1.0 eq.) of N-benzyl-N-(4-phenoxybenzyl)-amine-HCl in 50 mL of toluene was added 100 mL of 4 N aqueous NaOH, and the mixture was vigorously stirred until all of the solid dissolved (~30 minutes). To the resulting clear, biphasic mixture was added 7.8 mL of a 1.93 M solutuon of phosgene in toluene (15 mmol, 1.5 eq.) dropwise. A precipitate formed immediately, and the mixture was vigorously stirred until all of the solid had dissolved (~ 30 minutes). The layers were

separated, and the organic phase was dried, filtered and concentrated to give an oil that solidified on standing (3.42 g, 97%). This material was used without further purification. ^{1}H NMR (300 MHz., $CDCl_3$) δ 7.47 (m, 4H), 7.25 (m, 6H), 7.13 (m, 1H), 7.02 (m, 3H), 4.63 (d, 2H), 4.52 (d, 2H). MS (DCI, NH_3) m/e 370, 351, 290, 224, 217, 200, 183.

Example 122F

4-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]-2-methoxycarbonylmethoxybenzoic acid methyl ester

To a stirred solution of 175 mg (0.63 mmol, 1.0 eq.) of the compound resulting from Example 122D in 2 mL of pyridine was added sequentially, 19 mg (0.16 mmol, 0.25 eq.) of DMAP and 268 mg (0.76 mmol, 1.2 eq.) of the compound resulting from Example 122E, and the mixture was stirred at room temperature for 5 hours, at 55 °C for 16 hours and 24 hours at 100 °C. The cooled reaction mixture was poured into 3 N aqueous HCl and extracted with 3 portions of ethyl ether. The combined organic extracts were washed 3x with 3 N aqueous HCl and once with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on SiO_2 (20 g) eluting with 40% ethyl acetate in hexanes to give 25 mg (7%) of the title compound as an oil. ^{1}H NMR (300 MHz., $CDCl_3$) δ 7.76 (d, 1H), 7.24 - 7.43 (m, 10H), 7.12 (m, 1H), 7.01 (m, 4H), 6.52 (m, 2H), 4.73 (s, 2H), 4.60 (s, 4H), 3.87 (s, 3H), 3.81 (s, 3H). MS (DCI, NH_3) m/e 572 (40%); 555 (18%); 290 (100%); 283 (78%).

Example 122G

4-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]-2-carboxymethoxybenzoic acid

Using the procedure described in Example 112 and the compound resulting from Example 122F, the title compound was prepared as a lyophilate. ^{1}H NMR (300 MHz., $CDCl_3$) δ 7.92 (d, 1H), 7.24 - 7.43 (m, 10H), 7.12 (m, 1H), 7.01 (m, 4H), 6.52 (m, 1H), 4.82 (s, 2H), 4.63 (s, 4H). MS (FAB$^+$) m/e 527 (45%); 509 (39%); 183 (20%); 154 (100%); 136 (80%). Anal calcd for $C_{30}H_{26}N_2O_7 \cdot 1.26\ H_2O$: C, 68.43; H, 4.98; N, 5.32. Found: C, 65.69; H, 5.44; N, 4.53.

Example 123

5-[N-Benzyl-N-4-phenoxybenzylaminocarbonylamino]-2-carboxymethoxybenzoic acid

The title compound was prepared starting with 5-aminosalicylic acid and using the procedures described in Example 122. ^{1}H NMR (300 MHz., $CDCl_3$) δ 7.62 (m, 2H), 7.21 - 7.46 (m, 8H), 7.11 (m, 1H), 7.02 (m, 5H), 6.88 (m, 1H), 6.40 (bs, 1H), 4.74 (bs, 2H), 4.61 (m, 4H). MS (FAB+) m/e 527 (37%); 307 (22%); 183 (18%); 155 (26%); 154 (100%); 136 (67%). Anal calcd for $C_{30}H_{26}N_2O_7 \cdot 0.23\ H_2O$: C, 68.43; H, 4.98; N, 5.32. Found: C, 67.91; H, 5.27; N, 5.33.

Example 124

4-[1-(4-Phenoxyphenyl)-2-phenylethoxy]benzene-1,2-dicarboxylic acid

Example 124A

1-(4-Phenoxyphenyl)-2-phenylethanol

To a solution of 595 mg (3 mmol, 1 eq.) of 4-phenoxybenzaldehyde in 6 mL of THF at -10 °C was dropwise added 2.25 mL of a 2.0 M solution of benzylmagnesium chloride (4.5 mmol, 1.5 eq.) in THF. The solution was stirred at -10 °C for 1 hour and quenched by the careful addition of saturated aqueous NH_4Cl. The cloudy mixture was partitioned between dilute aqueous HCl and ethyl acetate. The organic phase was washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on SiO_2 (25 g) eluting with 10% ethyl acetate in hexanes to give 580 mg (67%) of the title compound as an oil. ^{1}H NMR (300 MHz., $CDCl_3$) δ 7.18 - 7.40 (m, 10H), 7.11 (m, 1H), 7.00 (m, 3H), 4.90 (m, 1H), 3.03 (dd, 1H), 3.01 (dd, 1H), 1.94 (bs, 1H). MS (DCI, NH_3) m/e 308 (12%); 290 (MH+, 63%); 273 (100%).

Example 124B

4-[1-(4-Phenoxyphenyl)-2-phenylethoxy]benzene-1,2-dicarboxylic acid dimethyl ester

To a stirred solution of 145 mg (0.5 mmol, 1.0 eq.) of the alcohol resulting from Example 124A in 8 mL of CH_2Cl_2 at 0 °C were sequentially added 210 mg (1.0 mmol, 2.0 eq.) of 4-hydroxydimethylphthalate and 328 mg (1.25 mmol, 2.5

eq.) of triphenylphosphine. To this solution was added a solution of 0.20 mL (1.25 mmol, 2.5 eq.) of diethyl azodicarboxylate in 2 mL of CH_2Cl_2 dropwise. The yellow solution was stirred for 1 hour at 0 °C and for 30 minutes at room temperature. The reaction mixture was concentrated to dryness and the residue purified by column chrmoatography on SiO_2 (20 g) eluting with 15% ethyl acetate in hexanes to give 130 mg (54%) of the title compound as a thick oil. ^1H NMR (300 MHz., $CDCl_3$) δ 7.67 (d, 1H), 7.34 (m, 2H), 7.07 - 7.30 (m, 8H), 7.01 (m, 3H), 6.93 (d, 2H), 6.86 (dd, 1H), 5.35 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.32 (dd, 1H), 3.11 (dd, 1H). MS (DCI, NH_3) m/e 500 (50%); 483 (100%); 292, (77%); 273 (63%); 239 (28%).

Example 124C

4-[1-(4-Phenoxyphenyl)-2-phenylethoxy]benzene-1,2-dicarboxylic acid

The title compound was prepared using the procedures described in Example 112 and the compound resulting from Example 124B. ^1H NMR (300 MHz., $CDCl_3$) δ 7.90 (m, 1H), 7.34 (m, 2H), 7.07 - 7.38 (m, 8H), 6.85 - 7.06 (m, 6H), 5.38 (m, 1H), 3.36 (bdd, 1H), 3.11 (bdd, 1H). MS (FAB^+) m/e 493 (10%; 477 (23%); 455 (30%); 273 (100%); 180 (58%); 154 (80%); 136 (66%). Anal cald for $C_{28}H_{22}O_6 \cdot 0.63$ EtOAc: C, 73.99; H, 4.88. Found: C, 71.89; H, 5.51.

Example 125

2-Allyloxycarbonyl-4,5-dicarboxylic anhydride-N-benzyl-n-(4-phenoxybenzyl)benzamide

Under N_2, a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.242 g, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C and subsequently treated in a dropwise manner with a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.289 g, 1.00 mmol) and DBU (0.171 g, 1.10 mmol) in anhydrous THF (10 mL). After 30 minutes allyl iodide (0.514 g, 3.00 mmol) was added, and the reaction mixture was allowed to warm to ambient temperature. After 14 hours the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (4 mL). The solution was extracted with 1 N aqueous HCl (2 x 3 mL), dried (Na_2SO_4), and then concentrated under reduced pressure to provide a tan foam. Flash column chromatography eluting

with 80:20 to 70:30 hexane:EtOAc afforded compound the title compound (0.065 g, 11% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, 2 H), 4.60-4.75 (m, 4 H), 5.22-5.42 (m, 2 H), 5.83-6.04 (m, 1 H), 6.85-7.40 (m, 15 H), 8.02 (m, 1 H). LRMS (DCI): 548 $(M+H)^+$.

Example 126a

2-Allyloxycarbonyl-4,5-dicarboxyl-N-benzyl-N-(4-phenoxybenzyl)-benzamide

and

Example 126b

2-Allyloxycarbonyl-4-benzyloxycarbonyl-5-carboxyl-N-benzyl-N-(4-phenoxybenzyl)-benzamide and

2-Allyloxycarbonyl-5-benzyloxycarbonyl-4-carboxyl-N-benzyl-N-(4-phenoxybenzyl)-benzamide

Under a N_2 atmosphere, a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.242 g, 1.00 mmol) in anhydrous MeCN (10 mL) was cooled to 0 °C and subsequently treated in a dropwise manner with a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.289 g, 1.00 mmol) and DBU (0.171 g, 1.10 mmol) in anhydrous MeCN (10 mL). After 30 minutes, allyl iodide (0.514 g, 3.00 mmol) was added, and the reaction mixture was heated to reflux for 4 hours. After cooling to ambient temperature, the reaction mixture was treated with benzyl alcohol (0.437 g, 4.00 mmol) and returned to reflux. After 14 hours the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (4 mL). The solution was extracted with 1 N aqueous HCl (5 x 2 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide a dark oil. Flash column chromatography on acidic silica gel, prepared by stirring in 2% H_3PO_4 in MeOH for 5 hours followed by filtration, eluting with 70:30 going to 60:40 hexane-EtOAc afforded, after lyophilization from CH_3CN-H_2O, a mixture of the title compounds 126b as a white powder (0.322 g, 49% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11-4.23 (m, 2H), 4.62-4.82 (m, 4H), 5.25-5.43 (m, 4H), 5.88-6.04 (m, 1H), 6.84-7.18 (m, 7H), 7.20-7.41 (m, 12H), 7.63 (m, 1H of one isomer), 7.82 (m, 1H of second isomer), 8.40 (m, 1H of second isomer), 8.52 (m, 1H of first isomer). LRMS (DCI) m/e 656 $(M+H)^+$. Further elution provided compound 126a (0.021 g, 4% yield). ^{1}H NMR (300

MHz, $CDCl_3$) δ 4.18 (d, 2H), 4.62-4.82 (comp, 4H), 5.23-5.42 (comp, 2H), 5.95-6.03 (m, 1H), 6.95-7.40 (comp, 14H), 7.70 (s, 1H), 8.50 (s, 1H), 10.58 (br s, 2H). LRMS (DCI) m/e 566 $(M+H)^+$.

Example 127

2-Allyloxycarbonyl-4,5-dibenzyloxycarbonyl-N-benzyl-N-(4-phenoxybenzyl)-benzamide

Under a N_2 atmosphere, a solution of the compounds resulting from Example 125 and 126a (0.141 g, 0.215 mmol), DBU (39.3 mg, 0.258 mmol), and benzyl bromide (45.0 mg, 0.258 mmol) in anhydrous MeCN (0.4 mL) was heated to reflux for 22 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 1:1 Et_20-EtOAc (4 mL). The solution was washed with saturated aqueous $NaHCO_3$ (4 x 2 mL) and 1 N aqueous HCl (5 x 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil. Radial chromatography eluting with 80:20 hexane-EtOAc afforded the title compound as a clear, viscous oil (94.0 mg, 59% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 4.07-4.22 (m, 2H), 4.61-4.80 (m, 4H), 5.18-5.43 (m, 6H), 5.85-5.99 (m, 1H), 6.88-7.40 (m, 24H), 7.70 (m, 1H), 8.41 (m, 1H). LRMS (DCI) m/e 746 $(M+H)^+$.

Example 128

3,4-Dibenzyloxycarbonyl-6-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-benzoic acid

Under a N_2 atmosphere, $Pd(PPh_3)_4$ (9.34 mg, 0.008 mmol, 10 mol %) was added to a solution of the compound resulting from Example 127 (60.0 mg, 0.08 mmol) and morpholine (70.4 mg, 0.8 mmol) in THF (0.80 mL). After 1 hour the reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (4 mL), and the solution was washed with 2 N aqueous HCl (4 x 2 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide an oil. Flash column chromatography on acidic silica gel, prepared by stirring in 2% H_3PO_4 in MeOH for 5 hours followed by filtration, eluting with 70:30 hexane-EtOAc afforded, after lyopholization from CH_3CN-H_2O, the title compound as a white powder (32.3

mg, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (d, J = 16.3Hz, 2H), 4.52-4.90 (br, 1H), 5.19-5.25 (m, 4H), 6.83-7.14 (m, 6H), 7.21-7.40 (m, 19H), 7.71 (m, 1H), 8.43 (m, 1H). LRMS (DCI) m/e 706 $(M+H)^+$.

Example 129

3-Benzyloxycarbonyl-6-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,4-dibenzoic acid and

4-Benzyloxycarbonyl-6-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,3-dibenzoic acid

Under a N_2 atmosphere, a solution of benzyl alcohol (0.109 g, 1.00 mmol) and triethylamine (0.102 g, 1.00 mmol) in THF (5 mL) was added dropwise to a solution of 4,5-dichlorocarbonylphthalic anhydride (0.136 g, 0.500 mmol) in THF (5 mL) at -30 °C. After 30 minutes, a solution of N-benzyl-N-(4-phenoxybenzyl)amine (0.145 g, 0.500 mmol) and Et_3N (51.5 mg, 0.500 mmol) in THF (2.5 mL) was added, and the reaction mixture was allowed to warm to ambient temperature. After 45 minutes, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (5 mL). The solution was washed with 1 N aqueous HCl (2 x 2 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide crude product as a white foam. Flash column chromatography on acidic silica gel, prepared by stirring in 2% H_3PO_4 in MeOH for 5 hours followed by filtration, eluting with 70:30 going to 60:40 hexane-EtOAc afforded a mixture of the title compounds as a white powder (0.109 g, 35% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15-4.25 (m, 2H), 4.25-5.25 (br, 2H), 5.28-5.30 (m, 2H), 6.82-7.10 (comp, 9H), 7.20-7.40 (comp, 15H), 7.64-7.80 (m, 1H), 8.25-8.32 (m, 1H), 10.05 (br, 2H). LRMS (DCI): 616 $(M+H)^+$.

Example 130

5-[N-(2-Ethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-Ethoxybenzyl-N-(4-phenoxybenzyl) amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl) amine substituting 2-ethoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2-ethoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.2 (dt, 3H), 3.90 (dq, 2H), 4.20 (d, 2H), 4.60 (s, 2H), 6.80 - 7.25 (m, 13H), 7.90 (s, 1H), 8.45 (s, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 131

5-[N-(3-Methylbenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-3-Methylbenzyl-N-(4-phenoxybenzyl)amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 3-methylbenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3- methylbenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.8 (s, 3H), 4.20 (d, 2H), 4.75 (s, 2H), 6.70 -7.60 (m, 13H), 7.80 (d, 1H), 8.45, (d, 1H). MS (FAB)$^+$ m/e 556 (M+H)$^+$ and (FAB)$^-$ m/e 554 (M-H)$^-$.

Example 132

5-[N-(2,3-Dimethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2,3-Dimethoxybenzyl-N-(4-phenoxybenzyl)amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2,3-dimethoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2,3-dimethoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.70 (s, 3H), 3.80 (s, 3H), 4.20 (d, 2H), 4.70 (s, 2H), 6.80 - 7.45 (m, 12H), 7.60 (s, 1H), 8.25 (s, 1H). MS (FAB)$^+$ m/e 586 (M+H)$^+$ and (FAB)$^-$ m/e 584 (M-H)$^-$.

Example 133

5-[N-(4-Methoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-4-Methoxybenzyl-N-(4-phenoxybenzyl)amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 4-methoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(4- methoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.75 (s, 3H), 4.20 (s, 2H), 4.60 (b, 2H), 6.80 - 7.45 (m, 13H), 7.70 (d, 1H), 8.35 (s, 1H). MS (FAB)$^+$ m/e 556 (M+H)$^+$ and (FAB)$^-$ m/e 554 (M-H)$^-$.

Example 134

5-[N-(2,6-Dimethoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2,6-Dimethoxybenzyl-N-(4-phenoxybenzyl)amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2,6-dimethoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4using N-(2,6-dimethoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.65 (s, 6H), 4.15 (d, 2H), 4.50 (s, 2H), 6.40 - 7.45 (m, 12H), 7.90 (s, 1H), 8.45 (s, 1H). MS (FAB)$^+$ m/e 586 (M+H)$^+$.

Example 135

5-[N-(2-n-Hexoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-n-Hexoxybenzyl-N-(4-phenoxybenzyl) amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 2-n-hexoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- n-hexoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.90

(m, 3H), 1.20 - 1.60 (m, 6H), 3.80 - 4.00 (m, 2H), 4.20 (d, 2H), 4.70 (s, 2H), 6.80 - 7.25 (m, 13H), 7.90 (s, 1H), 8.45 (s, 1H). MS (FAB)$^+$ m/e 626 (M+H)$^+$ and (FAB)$^-$ m/e 624 (M-H)$^-$.

Example 136

5-[N-(2-Phenoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-Phenoxybenzyl-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 2-phenoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- phenoxybenzyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (d, 2H), 4.65 (s, 2H), 6.60 - 7.85 (m, 18H), 7.95 (d, 1H), 8.50 (d, 1H). MS (FAB)$^+$ m/e 618 (M+H)$^+$ and (FAB)$^-$ m/e 616 (M-H)$^-$.

Example 137

5-[N-(2-Phenoxyethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-Phenoxyethyl-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 2-phenoxyethyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2-phenoxyethyl)-N-(4-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.20 - 3.40 (m, 2H), 4.0 (m, 2H), 4.20 (s, 2H), 6.80 - 7.45 (m, 13H), 7.85 (s, 1H), 8.25 (s, 1H). MS (FAB)$^+$ m/e 618 (M+H)$^+$ and (FAB)$^-$ m/e 616 (M-H)$^-$.

Example 138

5-[N-(2-Methoxyphenethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-Methoxyphenethyl-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-methoxyphenethyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- methoxyphenethyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 - 3.00 (m, 4H), 3.40 (s, 3H), 4.15 (s, 2H), 6.70 - 7.45 (m, 13H), 7.45 (s, 1H), 8.25 (s, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 139

5-[N-(2-Ethoxybenzyl)-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-Ethoxybenzyl-N-(3-phenoxybenzyl)amine was prepared using the procedure described for N-benzyl-N-(4-phenoxybenzyl)-amine substituting 2-ethoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- ethoxybenzyl)-N-(3-phenoxybenzyl)-amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.20 (m, 3H), 3.80 -4.00 (m, 2H), 4.20 (d, 2H), 4.60 (s, 2H), 6.80 - 7.50 (m, 13H), 7.55 (d, 1H), 8.25 (d, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 5.68 (M-H)$^-$.

Example 140

5-[N-(1,4-Benzodioxan-2-ylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(1,4-Benzodioxan-2-ylmethyl)-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 1,4-benzodioxan-2-ylmethyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(1,4-benzodioxan-2-ylmethyl)-N-(4-phenoxybenzyl)amine

in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.10 (m, 1H), 4.20 (t, 2H), 4.70 (s, 2H), 6.80 - 7.35 (m, 13H), 7.40 (m, 1H), 7.70 (m, 1H). MS (FAB)$^-$ m/e 580 (M-H)$^-$.

Example 141

5-[N-(3-Phenoxypropyl)-N-(4-phenoxybenzyl)aminocarbonyl] benzene-1,2,4-tricarboxylic acid

N-3-Phenoxypropyl-N-(4-phenoxybenzyl) amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 3-phenoxypropyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3- phenoxypropyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.10 -3.10 (m, 6H), 4.15 (m, 2H), 6.80 - 7.45 (m, 14H), 7.85 (m, 1H), 8.25 (m, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 142

5-[N-(2-(2-Ethoxyphenoxy)ethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-2-(2-Ethoxyphenoxy)ethyl-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-(2-ethoxyphenoxy)ethylamine for benzylamine.

The title compound was prepared by the procedures described in Example 4 using N-(2-(2-ethoxyphenoxy)ethyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.25 (m,3H), 4.00-4.20 (m, 6H), 4.50 (s, 2H), 6.80 - 7.65 (m, 13H), 8.10 (s, 1H), 8.80 (d, 1H). MS (FAB)$^-$ m/e 598 (M-H)$^-$.

Example 143

5-[N-(2-Phenoxyethyl)-N-(3-(4-methylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Phenoxyethyl)-N-(3-(4-methylphenoxy)benzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-phenoxyethylamine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2- phenoxyethyl)-N-(3-(4-methylphenoxy)benzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.95 (s, 3H), 3.95 - 4.20 (m, 2H), 4.40 (m, 2H), 6.80 - 7.30 (m, 13H), 7.95 (s, 1H), 8.40 (s, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 144

5-[N-(3-(2-Methoxyphenyl)propyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(3-(2-Methoxyphenyl)propyl)-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 3-(2-methoxyphenyl)propylamine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3-(2-methoxyphenyl)propyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.20 - 3.00 (m, 6H), 3.60 (s, 3H), 3.80 (s, 2H), 6.60 - 7.45 (m, 13H), 7.75 (m, 1H), 8.20 (m, 1H). MS (FAB)$^-$ m/e 582 (M-H)$^-$.

Example 145

5-[N-(3-Phenyl-2-propenyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(3-Phenyl-2-propenyl)-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 3-phenyl-2-propenyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(3-phenyl-2-propenyl)-N-(4-phenoxybenzyl)amine in place

of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.35 (m, 2H), 3.60 (t, H), 3.80 (d, H), 4.25 (d, 2H), 6.80 - 7.25 (m, 13H), 7.90 (s, 1H), 8.45 (s, 1H). MS (FAB)$^-$ m/e 550 (M-H)$^-$.

Example 146

5-[N-Benzyl-N-(2-phenoxyethyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N- Benzyl-N-(2-phenoxyethyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-phenoxyethyl amine for 4-phenoxybenzyl amine.

The title compound was prepared by the procedures described in Example 4 using N- benzyl-N-(2-phenoxyethyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.20 (m, 2H), 4.20 (t, 2H), 4.40 (s, 2H), 6.80 - 7.35 (m, 10H), 7.80 (s, 1H), 8.30 (s, 1H). MS (FAB)$^+$ m/e 464 (M+H)$^+$ and (FAB)$^-$ m/e 462 (M-H)$^-$.

Example 147

4-[N-(2-Methoxybenzyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

N-(2-Methoxybenzyl)-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-methoxybenzyl amine for benzyl amine.

The title compound was prepared by the procedures described in Example 4 using N-(2-methoxybenzyl)-N-(4-phenoxybenzyl)amine in place of N-benzyl-N-(4-phenoxybenzyl)amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.70 (s, 3H), 4.40 (m, 2H), 4.60 (m, 2H), 6.80 - 7.45 (m, 14H), 7.65 (m, 1H), 7.80 (m, 1H). MS (FAB)$^+$ m/e 512 (M+H)$^+$ and (FAB)$^-$ m/e 510 (M-H)$^-$.

Example 148

5-[N-(2-Ethoxybenzyl)-N-(3-(4-methylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

N-(2-Ethoxybenzyl)-N-[3-(4-methylphenoxy)benzyl]amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-ethoxybenzyl amine for benzyl amine and 3-(4-methylphenoxy)benzaldehyde for 4-phenoxybenzaldehyde.

To a solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.43 g, 0.002 mol) in 50 mL of tetrahydrofuran cooled in a salt - ice bath was added N-methylmorpholine (0.21 g, 0.002 mol). To this mixture was added a solution of N-(2-ethoxybenzyl)-N-[3-(4-methylphenoxy)benzyl]amine (0.69 g, 0.002 mol) contained in 10 mL of tetrahydrofuran dropwise over 3 hours via syringe pump. After stirring an additional hour, the reaction mixture was evaporated under reduced pressure at room temperature. EtOAc was added and the resulting solution washed with 5% HCl followed by a saturated solution of NaCl and concentrated under reduced pressure. A saturated solution (40 mL) of Na_2CO_2 and tetrahydrofuran (10 mL) were added and the reaction mixture stirred at room temperature for 12 hours. The tetrahydrofuran was evaporated; the basic solution acidified and extracted with ethyl acetate. The crude residue was then purified by flash silica gel chromatography eluting with with 95:4:1 $CHCl_3$-MeOH-HOAc to afford 0.98 g (83.9%) of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.20 (dt, 3H), 1.90 (s, 3H), 3.90 (dq, 2H), 4.20 (d, 2H), 4.65 (s, 2H), 6.80-7.50 (m, 12H), 7.55 (s, 1H), 8.25 (d, 1H). MS $(FAB)^+$ m/e 584 $(M+H)^+$ and $(FAB)^-$ m/e 582 $(M-H)^-$.

Example 149

5-{N-(2-Methoxybenzyl)-N-[3-(4-methylphenoxy)benzyl] aminocarbonyl}benzene-1,2,4-tricarboxylic acid

N-2-Methoxybenzyl-N-[3-(4-methylphenoxy)benzyl]amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-methoxybenzyl amine for benzyl amine and 3-(4-methylphenoxy)benzaldehyde for 4-phenoxybenzalde.

The title compound was prepared by the procedures described in Example 148 using N-(2-methoxybenzyl)-N-[3-(4-phenoxy)benzyl]amine in place of N-2-ethoxybenzyl-N-[3-(4-methylphenoxy)benzyl]amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.90 (s, 3H), 3.60 (m, 3H), 4.20 (d, 2H), 4.60 (bs, 2H), 6.80 - 7.45 (m, 12H), 7.70 (s, 1H), 8.35 (s, 1H). MS (FAB)$^+$ m/e 570 (M+H)$^+$ and (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 150

5-{N-Benzyl-N-(3-chloro-4-phenoxybenzyl)aminocarbonyl}benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-[4-phenoxy-(3-chlorobenzyl)] amine was prepared using the same procedure as given for the preparation for N-Benzyl-N-(4-Phenoxybenzyl) amine except replacing the 4-phenoxybenzaldehyde with 4-phenoxy-3-chlorobenzaldehyde.

The title compound was prepared by the procedures described in Example 148 using N-benzyl-N-(3-chloro-4-phenoxybenzyl)amine in place of N-2-ethoxybenzyl-N-[3-(4-methylphenoxy)benzyl] amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.20 (d, 2H), 4.60 (b, 2H), 6.80 - 7.45 (m, 13H), 7.70 (d, 1H), 8.30 (s, 1H). MS (FAB)$^+$ m/e 560 (M+H)$^+$ and (FAB)$^-$ m/e 558 (M-H)$^-$.

Example 151

5-{N-(2-(3-Methylbutoxy)benzyl)-N-(4-phenoxybenzyl)aminocarbonyl}benzene-1,2,4-tricarboxylic acid

N-(2-(3-Methylbutoxy)benzyl)-N-(4-phenoxybenzyl)amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting N-(2-(3-methylbutoxy)benzyl)amine for benzyl amine.

The title compound was prepared by the procedures described in Example 148 using N-(2-(3-methylbutoxy)benzyl)-N-(4-phenoxybenzyl)amine in place of N-(2-ethoxybenzyl)-N-[3-(4-methylphenoxy)benzyl]amine. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.85 (dd, 6H), 3.80 - 4.00 (m, 5H), 4.20 (bd, 2H), 4.80 (bs, 2H), 6.80 - 7.45 (m, 13H), 7.70 (bs, 1H), 8.30 (bd, 1H). MS (FAB)$^+$ m/e 612 $(M+H)^+$ and (FAB)$^-$ m/e 610 $(M-H)^-$

Example 152

5-{N-(2-Ethoxybenzyl)-N-[3-(4-chlorophenoxy)benzyl]aminocarbonyl}benzene-1,2,4-tricarboxylic acid

N-2-Ethoxybenzyl-N-[3-(4-chlorophenoxy)benzyl]amine was prepared using the procedures described for N-benzyl-N-(4-phenoxybenzyl)amine substituting 2-ethoxybenzyl amine for benzyl amine and 3-(4-chlorophenoxy)benzaldehyde for 4-phenoxybenzaldehyde.

The title compound was prepared by the procedures described in Example 148 using N-(2-ethoxybenzyl)-N-[3-(4-chlorophenoxy)benzyl]amine in place of N-2-ethoxybenzyl-N-[3-(4-methylphenoxy)benzyl]amine . ^{1}H NMR (DMSO-d_6, 300 MHz), δ 1.20 (dt, 3H), 3.90 (dq, 2H), 4.20 (d, 2H), 4.65 (s,2H), 6.80 - 7.45 (m, 12H), 7.70 (m, 1H), 8.35 (m, 1H). MS (FAB)$^+$ m/e 604 $(M+H)^+$ and (FAB)$^-$ m/e 602 $(M-H)^-$.

Example 153

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]biphenyl-3,3',4'-tricarboxylic acid and

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]biphenyl-4,3',4'-tricarboxylic acid

The title compound mixture was prepared by the procedures described in Example 148 using N-benzyl-N-(4-phenoxybenzyl)amine in place of N-2-ethoxybenzyl-N-[3-(4-methylphenoxy)benzyl]amine and replacing the benzene dianhydride with 4,4'-biphthalic anhydride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.90 (d, 2H), 4.60 (b, 2H), 6.80 - 8.20 (m, 20H). MS (FAB)$^+$ m/e 602 (M+H)$^+$ and (FAB)$^-$ m/e 600 (M-H)$^-$.

Example 154

4-[N-Benzyl-N-(4-phenylbutyl)aminocarbonylmethyl]biphenyl-1,2-dicarboxylic acid

Example 154A

N- Benzyl-N-4-phenylbutylamine

To a solution of benzaldehyde (3.36 g, 31.2 mmol) and 4-phenylbutylamine (4.50 g, 30.1 mmol) in 60 mL of toluene was added a catalytic amount of p-toluenesulfonic acid. The reaction flask was fitted with a Dean Stark trap and heated to reflux for 16 hours. The solvent was then evaporated, and the reaction was taken up in 100 mL EtOH. Sodium borohydride (1.14 g, 30.1 mmol) was added, and the reaction was again heated to reflux until judged complete by TLC. The reaction mixture was evaporated, taken up in EtOAc and washed with 1 N aqueous NaOH, 1 N aqueous HCl, and then saturated aqueous NaCl solution, dried over sodium sulfate, filtered and evaporated to give 7.08 g (98%) of an oil and which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (bs, 1H), 1.50 - 1.71 (m, 4H), 2.58 - 2.68 (m, 4H), 3.77 (s, 2H), 7.13 - 7.38 (m, 10H). MS (DCI-NH_3) m/e 240 (M+H)$^+$.

Example 154B

4-[N-Benzyl-N-(4-phenylbutyl)aminocarbonylmethyl]biphenyl-1,2-dicarboxylic acid

A solution of trimellitic anhydride chloride (226 mg, 1.08 mmol), triethylamine (113mg, 1.12 mmol) and N-benzyl-N-(4-phenylbutyl)amine (365 mg, 1.12 mmol) in 10 mL of CH_2Cl_2 was stirred for 12 hours and then evaporated. The residue obtained was taken up in methanol and 100 mg of KOH was added. After 40 minutes, the reaction mixture was evaporated, 1 N HCl was added, and the reaction was titrated to pH = 3 and extracted 3 times with EtOAc. The organic layers were dried over sodium sulfate, filtered and evaporated to give an oil which was purified by silica gel chromatography eluting with 5% MeOH in $CHCl_3$ with 0.5% AcOH to give 141 mg (28%) of the title compound as a white foamy solid. ^1H NMR ($CDCl_3$, 300 MHz) mixture of amide rotamers δ 1.30 - 1.50 (m, 4H), 2.05 (s, 2H), 2.36 (bs, 1H), 2.60 (bs, 1H), 3.0 (bs, 1H), 3.4 (bs, 1H), 3.8 (bs, 1H), 4.66 (bs, 1H), 6.90 - 7.40 (m, 13H). MS (Cl-NH_3) m/e M^+, 431.

Example 155

4-[N-Benzyl-N-(5-phenylpentyl)aminocarbonylmethyl]benzene-1,2-dicarboxylic acid

Example 155A

N-Benzyl-5-phenylpentanamide

To a solution of 5-phenylpentanoic acid (4.43 mmol) in 20 mL of CH_2Cl_2 at room temperature was added oxalyl chloride (1.41 g, 11.08 mmol) and 1 drop of DMF, and the reaction mixture was stirred for 1 hour under nitrogen. The CH_2Cl_2 and excess oxalyl chloride were evaporated. The reaction was redissolved in CH_2Cl_2 and benzylamine (1.42 g, 13.3 mmol) and 2 mL of saturated aqueous $NaHCO_3$ were added and the reaction stirred for 12 hours. The reaction was taken up in EtOAc and washed with 1 N HCl x 2, followed by saturated aqueous NaCl, and evaporated to give an oil that was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 - 1.80 (m, 4H), 2.22 (t,

2H), 2.64 (t, 2H), 4.42 (d, 2H), 5.68 (bs, 1H), 7.12 - 7.35 (m, 10H) MS (Cl-NH_3) m/e MH^+, 268.

Example 155B

N-Benzyl-N-(5-phenylpentyl)amine

The compound resulting from Example 155A (4.33 mmol) was dissolved in THF and lithium aluminum hydride (8.66 mL, 1.0 M solutionn in THF) was added by syringe, and the reaction was heated to reflux for 6 hours under nitrogen. The reaction was cooled and quenched with water and 15% aqueous sodium hydroxide, then filtered and evaporated to give the title compound as an oil that was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 - 1.46 (m, 2 H), 1.50 - 1.68 (m, 4H), 2.57 - 2.65 (app q, 4H), 3.78 (s, 2H), 7.14 - 7.34 (m, 10 H). MS (DCI-NH_3) m/e 254 $(M+H)^+$.

Example 155C

4-[N-Benzyl-N-(5-phenylpentyl)aminocarbonylmethyl]benzene-1,2-dicarboxylic acid

The title compound was prepared using the compound resulting from Example 155B and the procedures described in Example 154B. ^1H NMR ($CDCl_3$, 300 MHz) mixture of amide rotamers δ 1.30 - 1.50 (m, 4H), 1.52 - 1.62 (m, 2H), 2.45 (bs, 1H), 2.55 (bs, 1H), 3.0 (bs, 1H), 3.4 (bs, 1H), 4.35 (bs, 1H), 4.71 (bs, 1H), 6.97 - 7.40 (m, 12H), 7.8 (bs, 1H). MS (DCI-NH_3) m/e 445 $(M+H)^+$.

Example 156

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

Example 156A

3-Carboxyphthalic anhydride

Benzene 1,2,3-tricarboxylic acid monohydrate (20 g, 95.2 mmol) and acetic anhydride (13.5 mL, 143 mmol) were stirred at reflux for 4 hours. The solution was cooled to 0 °C and the resulting white solid was collected by filtration and then Soxhlet-extracted over 48 hours with diethyl ether. The

filtrate was dried under high vacuum at 60 °C to provide 16.7 g (91%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (dd, 1H), 7.8 (dd, 1H), 8.1 (dd, 1H), 12.5 (br s, 1H). MS (DCI) m/e 210 $(M+NH_4)^+$.

Example 156B

3-Chloroformylphthalic anhydride

The compound resulting from Example 156A (6.34 g, 32.9 mmol) was treated with thionyl chloride (3.3 mL, 53.8 mmol) and DMF (6 µL) then stirred at 115 °C for 3 hours. Removal of volatiles under reduced pressure provided 6.9 g of the crude title compound as a yellow solid which was used without further purification in the next step.

Example 156C

2,6-Dimethoxycarbonylbenzoic acid (i) and

2,3-Dimethoxycarbonylbenzoic acid (ii)

A solution of the compound resulting from Example 156B (6.9 g, 32.9 mmol) and diisopropylethylamine (17.2 mL, 98.7 mmol) in methanol (66 mL) was stirred at -20 °C for 9 hours then at room temperature for 18 hours. The volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate (100 mL) and 6 N HCl (100 mL). The organic layer was dried ($MgSO_4$), filtered, treated with silica gel and concentrated to dryness. The mixture was slurried in 98:1:1 $CHCl_3$-MeOH-HOAc and added to a column made up of the same solvent system. Elution with 98:1:1 $CHCl_3$-MeOH-HOAc provided 3.09 g (39%) of 2,6-dimethoxycarbonylbenzoic acid (i) and 1.74 g (22%) of 2,3-dimethoxycarbonylbenzoic acid (ii). ^{1}H NMR (i) ($CDCl_3$, 300 MHz) δ 3.5 (s, 6H), 7.2 (dd, 1H), 7.6 (dd, 1H), 7.9 (dd, 1H), 12.5 (br s, 1H). MS (DCI) m/e 239 $(M+H)^+$. ^{1}H NMR (ii) ($CDCl_3$, 300 MHz) δ 3.5 (s, 3H), 3.6 (s, 3H), 7.5 (dd, 1H), 7.9 (dd, 1H), 8.0 (dd, 1H), 12.5 (br s, 1H). MS (DCI) m/e 239 $(M+H)^+$.

Example 156D

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,3-dimethoxycarbonylbenzene

A solution of the compound resulting from Example 156C (i) (543 mg, 2.3 mmol) in toluene (5 mL) was treated with oxalyl chloride (258 µL) and DMF (2 drops). After 18 hours, the solution was concentrated to dryness, and the acid chloride thus obtained was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a slurry of N-benzyl-N-(4-phenoxybenzyl)amine hydrochloride (1.1 g, 3.42 mmol) and $NaHCO_3$ (1.21 g, 11.4 mmol) in water (10 mL). After 18 hours, the CH_2Cl_2 layer was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 1.13 mg (97%) of the title compound as a white foam. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.9 (s, 6H), 4.7 (s, 2H), 5.6 (s, 2H), 7.0-7.4 (m, 14H), 7.6 (dd, 1H), 7.8 (dd, 1H), 8.0 (dd, 1H). MS (DCI) m/e 510 $(M+H)^+$.

Example 156E

2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

A solution of the compound resulting from Example 156D (1.1 g, 2.3 mmol) in THF (34 mL) and water (11 mL) was treated with 1 N LiOH (11.4 mL). After 18 hours, the solution was acidified to pH 0 with 1 N HCl, concentrated to remove the THF, and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated, and the residue was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-HOAc to provide 87 mg (80%) of the title compound as a white solid. ^1H NMR DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 5.8 (s, 2H), 7.1-7.4 (m, 14H), 12.5 (br s, 2H). MS (DCI) m/e 482 $(M+H)^+$.

Example 157
2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,3-dicarboxylic acid

Example 157A
N-Benzyl-N-(4-phenoxybenzyl)-N'-(2,6-dimethoxycarbonylphenyl)urea

A solution of 2,6-dimethoxycarbonylbenzoic acid (500 mg, 2 mmol) in toluene (5 mL) was treated with diphenylphosphoryl azide (643 mg, 2.34 mmol) and triethylamine (644 mg, 2.3 mmol) then warmed to 80 °C for 18 hours. N-Benzyl-N-(4-phenoxybenzyl)amine hydrochloride (1.04 g, 3.2 mmol) was added, and the brown reaction mixture was stirred an additional 18 hours. Volatiles were removed, and the residue was dissolved in ethyl acetate and washed with 1 N HCl, half saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel eluting with 15% ethyl acetate in hexane to provide 99 mg (90%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.4 (s, 6H), 4.6 (s, 2H), 5.1 (s, 2H), 6.1 (br s, 1H), 7.2-7.5 (m, 14H), 7.6 (dd, 1H), 7.8 (dd, 1H), 8.0 (dd, 1H). MS (DCI) m/e 525 $(M+H)^+$.

Example 157B
2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,3-dicarboxylic acid

The compound resulting from Example 157A (99 mg, 2.1 mmol) in water (10 mL) and THF 32 mL) was treated with 1 N LiOH (10.6 mL) and stirred for 18 hours. The solution was acidified to pH 0 with 1 N HCl and concentrated to remove THF. The water layer was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide a residue which was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-HOAc to provide 90 mg (96%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.7 (s, 2H), 5,2 (s, 2H), 6.3 (br s, 1H), 7.2-7.5 (m, 14H), 7.6 (dd, 1H), 7.8 (dd, 1H), 8.1 (dd, 1H), 12.7 (br s, 2H). MS (DCI) m/e 497 $(M+H)^+$.

Example 158

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,2-dicarboxylic acid dimethyl ester

A solution of 2,3-dimethoxycarbonylbenzoic acid (421 mg, 1.7 mmol) in toluene (5 mL) was treated with diphenylphosphoryl azide (535 mg, 1.94 mmol) and triethylamine (358 mg, 3.54 mmol) and then warmed to 80 °C for 18 hours. N-Benzyl-N-(4-phenoxybenzyl)amine hydrochloride (577 mg, 1.77 mmol) was added, and the brown reaction mixture was stirred an additional 18 hours. The volatiles were removed, and the residue was dissolved in ethyl acetate and washed with 1 N HCl, half saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with 20% ethyl acetate in hexane to provide 750 mg (83%) of the title compound as a colorless glass. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.5 (s, 3H), 3.6 (s, 3H), 4.4 (s, 2H), 5.6 (s, 2H), 6.2 (s, 1H), 7.0-7.7 (m, 14H), 7.2 (dd, 1H), 7.6 (dd, 1H), 7.9 (dd, 1H). MS (DCI) m/e 525 $(M+H)^+$.

Example 159

4-[2-Benzyl-3-(4-phenoxyphenyl)propionylamino]benzene-1,2-dicarboxylic acid

Example 159A

Methyl 4-phenoxycinnamate

A slurry of NaH (4 g, 0.1 mol) in THF (200 mL) at 0 °C was treated with methyl dimethylphosphonoacetate (21.8 g, 0.12 mol) and stirred for 1 hour. 4-Phenoxybenzaldehyde was added to the mixture, and stirring was continued for 18 hours. The volatiles were removed under reduced pressure, and the residue was partitioned between water (500 mL) and ethyl acetate (500 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to provide a white solid which was used directly in the next step without further purification. ^1H NMR ($CDCl_3$, 300 mHz) δ 3.7 (s, 3H), 6.25 (s, 1H), 6.51 (s, 1H), 6.9-7.1 (m, 4H), 7.1-7.3 (m, 3H), 7.3-7.4 (m, 2H). MS (DCI) m/e 255 $(M+H)^+$.

Example 159B

Methyl 3-(4-phenoxyphenyl)propionate

A mixture of the compound resulting from Example 159A (20 g, 78.7 mmol), ammonium formate (49.5 g, 786 mmol) and 10% Pd on carbon (5 g) was warmed to reflux for 18 hours, cooled to room temperature, filtered through celite, concentrated and chromatographed eluting with 10% ethyl acetate in hexane to provide 20 g (99%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.6 (t, 2H), 2.9 (t, 2.9), 3.7 (s, 3H), 6.9-7.1 (m, 4H), 7.1-7.3 (m, 3H), 7.3-7.5 (m, 2H). MS (DCI) m/e 257 $(M+H)^+$.

Example 159C

Methyl 2-benzyl-3-(4-phenoxyphenyl)propionate

A solution of 0.5 M potassium bis(trimethylsilyl)amide in toluene (36.7 mL) at -78 °C was treated via cannula with a -78 °C solution of the compound resulting from Example 159B (4.3 g, 16.7 mmol) in THF (56 mL). After 1 hour at -78 °C, the enolate solution was treated with benzyl bromide (11.43 g, 66.8 mmol) and stirred for an additional 10 hours. The reaction was quenched with saturated ammonium chloride, and the THF was removed under reduced pressure. The water layer was extracted with ethyl acetate (2 x 100 mL), and the combined extracts were dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed eluting with 10% ethyl acetate in hexane to provide 800 mg (14%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.8 (m, 2H), 3.0 (m, 3H), 3.5 (s, 3H), 6.9-7.4 (m, 14H). MS (DCI) m/e 347 $(M+H)^+$.

Example 159D

2-Benzyl-3-(4-phenoxyphenyl)propionic acid

The compound resulting from Example 159C in methanol (12 mL) and water (3 mL) at room temperature was treated with 87% KOH (680 mg, 10.4 mmol) in water (5 mL). After 18 hours, the solution was acidified to pH 0 with 1 N HCl and concentrated to remove methanol. The resulting suspension was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide an oil which was used in

the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.7 (m, 2H), 3.1 (m, 3H), 6.9-7.4 (m, 14H), 12.0 (br s, 1H). MS (DCI) m/e 333 $(M+H)^+$.

Example 159E

4-[2-Benzyl-3-(4-phenoxyphenyl)propionylamino]benzene-1,2-dicarboxylic acid dimethyl ester

A solution of the compound resulting from Example 159D (774 mg, 2.3 mmol) in toluene (2 mL) was treated with oxalyl chloride (32.5 mg, 2.6 mmol) and DMF (2 drops). After 18 hours, the solution was concentrated to dryness, and the acid chloride thus obtained was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a slurry of 4-amino-1,2-dimethylphthalate (562 mg, 2.3 mmol) and $NaHCO_3$ (247 mg, 2.3 mmol) in water (5 mL). After 18 hours, the CH_2Cl_2 layer was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 25% ethyl acetatein hexane to provide 1.01 g (83%) of the title compound as a colorless glass. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.7 (m, 1H), 2.9 (m, 2H), 3.05 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.8 (s, 1H), 7.05-7.45 (m, 16H), 7.65 (d, 1H). MS (DCI) m/e 524 $(M+H)^+$.

Example 159F

4-[2-Benzyl-3-(4-phenoxyphenyl)propionylamino]benzene-1,2-dicarboxylic acid

A solution of the compound resulting from Example 159E (90 mg, 0.17 mmol) in MeOH (1 mL) and water (1 mL) at room temperature was treated with 87% KOH (109 mg, 1.7 mmol) in water (1 mL). After 18 hours, the methanol was removed, and the aqueous solution was acidified to pH 0 with 1 N HCl. The suspension was extracted with ethyl acetate (2 x 5 mL), and the combined extracts were dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 98:1:1 $CHCl_3$-MeOH-HOAc to provide 80.3 mg (95%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.7 (m, 2H), 3.0 (m, 3H), 6.8 (m, 5H), 7.1-7.4 (m, 10H), 7.5-7.7 (m, 3H), 12.0 (br s, 2H). MS (DCI) m/e 496 $(M+H)^+$.

Example 160

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

Example 160A

4-Nitrobenzene-1,3-dicarboxylic acid

Potassium permanganate (262 g, 1.66 mol) was added portionwise over 6 hours to a solution of of 5-methyl-2-nitrobenzoic acid (112.3 g, 0.62 mol) and sodium hydroxide (25.6 g, 0.62 mol) in water (1.5 L) at 90 °C. After 6 hours, the solution was cooled to room temperature and filtered through celite. The filtrate was acidified with 12 N HCl (500 mL) and refrigerated for 18 hours. The resulting solid was filtered and dried under high vacuum to provide 128.7 g (98%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (dd, 1H), 8.8 (d, 1H), 8.9 (d, 1H), 12.0 (br s, 2H). MS (DCI) m/e 212 $(M+H)^+$.

Exampe 160B

Dimethyl 4-nitroisophthalate

The compound resulting from Example 160A (96 g, 0.455 mol) in methanol (1L) was treated with concentrated sulfuric acid (100 mL) and refluxed for 18 hours. The volume of methanol was reduced to ~200 mL, and the hot solution was treated with water until turbid. The suspension was refrigerated for 18 hours and then filtered to provide 93 g (85%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 3H), 3.85 (s, 3H), 8.25 (dd, 1H), 8.8 (d, 1H), 8.9 (d, 1H). MS (DCI) m/e 240 $(M+H)^+$.

Example 160C

Dimethyl 4-aminoisophthalate

A slurry of the compound resulting from Example 160B (20 g, 83.7 mmol), ammonium formate (52 g, 837 mmol) and palladium on carbon (5 g) in methanol (500 mL) was stirred at reflux for 3 hours, cooled, filtered and concentrated to provide the title compound as a yellow solid which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s,

3H), 3.85 (s, 3H), 4.2 (s, 2H), 8.0 (dd, 1H), 8.6 (dd, 1H), 8.8 (d, 1H). MS (DCI) m/e 210 $(M+H)^+$.

Example 160D

Dimethyl 4-iodoisophthalate

A slurry of the compound resulting from Example 160C (8.5 g, 40.7 mmol) in 2% HCl (150 mL) at 0 °C was treated with sodium nitrite (3.1 g, 44.8 mmol) followed by potassium iodide (10.1 g, 61.1 mmol). The brown slurry was stirred for 1 hour at 0 °C and then treated with sodium sulfite (300 g). The yellow slurry was extracted with ethyl acetate (3 x 250 mL), and the combined extracts were dried ($MgSO_4$), filtered and concentrated to provide a yellow oil. Chromatography of the oil on silica gel eluting with ethyl acetate/hexane provided 5.1 g (39%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 3H), 3.85 (s, 3 H), 7.9 (dd, 1H), 8.6 (dd, 1H), 8.7 (d, 1H). MS (DCI) m/e 321 $(M+H)^+$.

Example 160E

Dimethyl 4-vinylisophthalate

A solution of the compound resulting from Example 160D (2.0 g, 6.2 mmol), vinyltributyltin (2.4 g, 7.5 mmol) and tetrakistriphenylphosphine-palladium(0) (36 mg) were stirred in toluene (30 mL) at 100 °C for 18 hours. The solution was then cooled to 0 °C, treated with 1:1 water-DBU (10 mL) and filtered through celite. The layers were separated, and the organic fraction was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel eluting with 5% ethyl acetate in hexane to provide 620 mg (48%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H), 4.0 (s, 3H), 5.45 (dd, 1H), 5.8 (dd, 1H), 7.7 (m, 1H), 7.9 (dd, 1H), 8.6 (dd, 1H), 8.7 (d, 1H). MS (DCI) m/e 221$(M+H)^+$.

Example 160F

2,4-Dimethoxycarbonylbenzoic acid

A suspension of the compound resulting from Example 160E (302 mg, 1.4 mmol), ruthenium trichloride (14.2 mg, 0.069 mmol) and sodium periodate (1.46 g, 6.85 mmol) in 1:1:1.5 CCl_4-CH_3CN-H_2O (10.5 mL) was stirred at 60 °C for 2 hours. The reaction mixture was cooled to room temperature and filtered through celite. The layers were separated, and the organic layer was dried ($MgSO_4$), filtered and concentrated. The white residue thus obtained (326 mg, 99%) was used without further purification in the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 3H), 3.9 (s, 3H), 8.2 (dd, 1H), 8.7 (dd, 1H), 8.8 (dd, 1H), 12.0 (br s, 1H). MS (DCI) m/e 239 $(M+H)^+$.

Example 160G

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-1,3-dimethoxycarbonylbenzene

A solution of the compound resulting from Example 160F (286 mg, 1.2 mmol) in toluene (4 mL) was treated with oxalyl chloride (184 mg, 1.4 mmol) and DMF (2 drops) then stirred for 18 hours. The toluene was removed, and the acid chloride thus obtained was dissolved in CH_2Cl_2 (5 mL) and added to a slurry of N-benzyl-N-(4-phenoxybenzyl)amine (347 mg, 1.2 mmol) and $NaHCO_3$ (1.27 g, 12 mmol) in water (5 mL). After 18 hours, the layers were separated, and the organic layer was dried ($MgSO_4$), filtered, concentrated and chromatographed eluting with 20% ethyl acetate in hexane to provide 600 mg (99%) of the title compound as a colorless glass. ^1H NMR (CDC_3, 300 MHz) δ 3.8 (s, 3H), 3.85 (s, 3H), 4.6 (s, 2H), 4.65 (s, 2H) 7.0-7.4 (m, 14H), 8.2 (dd, 1H), 8.65 (d, 1H), 8.8 (d, 1H). MS (DCI) m/e 510 $(M+H)^+$.

Example 160H

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

A solution of the compound resulting from Example 160G (600 mg, 1.2 mmol) in water (1 mL) and MeOH (3 mL) was treated with 87% KOH (76 mg, 11.8 mmol) in water (1 mL) and stirred for 18 hours. The MeOH was removed, and the resulting suspension was extracted with ethyl acetate (2 x 5 mL). The ethyl acetate was dried ($MgSO_4$), filtered and concentrated to provide an oil. Chromatography of the oil eluting with 98:1:1 $CHCl_3$-MeOH-HOAc provided 560 g (98%) of the title compound as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.5 (s, 2H), 4.55 (s, 2H), 7.0-7.4 (m, 14H), 8.1 (dd, 1H), 8.6 (d, 1H), 8.8 (d, 1H), 12.0 (br s, 2H). MS (DCI) m/e 482 $(M+H)^+$.

Example 161

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,3-dicarboxylic acid

Example 161A

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,3-dicarboxylic acid dimethyl ester

A solution of 2,4-dimethoxycarbonylbenzoic acid (301 mg, 1.3 mmol) in toluene (4 mL) was treated with diphenylphosphoryl azide (383 mg, 1.4 mmol) and triethylamine (255 mg, 2.5 mmol) and stirred 18 hours at 80 °C. N-Benzyl-N-(4-phenoxybenzyl)amine (472 mg, 1.63 mmol) was then added to the reaction mixture, and stirring was continued for an additional 18 hours. The reaction mixture was cooled to room temperature, washed with 1 N HCl (10 mL), half-saturated $NaHCO_3$ (10 mL) and brine (10 mL), and concentrated to dryness. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to provide 650 mg (98%) of the title compound as a colorless glass. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.8 (s, 3H), 3.85 (s, 3H), 3.95 (s, 2H), 4.0 (s, 2H), 4.1 (d, 1H), 6.9-7.45 (m, 14H), 8.2 (m, 2H), 8.65 (dd, 1H). MS (DCI) m/e 525 $(M+H)^+$.

Example 161B

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,3-dicarboxylic acid

A solution of the compound resulting from Example 161A (650 mg, 1.2 mmol) in water (1 mL) and MeOH (3 mL) was treated with 87% KOH in water (1 mL) and stirred for 18 hours. The MeOH was removed, and the resulting suspension was extracted with ethyl acetate (2 x 5 mL). The ethyl acetate was dried ($MgSO_4$), filtered and concentrated to provide an oil. Chromatography of the oil eluting with 98:1:1 $CHCl_3$-MeOH-HOAc provided 600 mg (98%) of the title compound as a white solid. ^1H NMR δ (DMSO-d_6, 300 MHz) δ 3.99 (s, 2H), 4.0 (s, 2H), 4.3 (d, 1H), 6.85-7.45 (m, 14H), 8.2 (m, 2H), 8.65 (m, 1H), 12.6 (brs, 2H). MS (DCI) m/e 497 $(M+H)^+$.

Example 162

5-[N-(2-Pyridylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Using the procedures described in Example 1 and substituting 2-pyridylmethylamine for benzylamine provided the title compound. ^1H NMR (DMSO-d_6, 500 MHz) δ 4.3 (m, 4H), 6.85-8.5 (m, 15H). MS m/e 527 $(M+H)^+$.

Example 163

5-[N-(3-Pyridylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Using the procedures described in Example 1 and substituting 3-pyridylmethylamine for benzylamine provided the title compound. ^1H NMR (DMSO-d_6, 500 MHz) δ 4.3 (m, 4H), 6.85-8.55 (m, 15H). MS m/e 527 $(M+H)^+$.

Example 164

5-[N-(4-Pyridylmethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Using the procedures described in Example 1 and substituting 4-pyridylmethylamine for benzylamine provided the title compound. ^1H NMR (DMSO-d_6, 500 MHz) δ 4.28 (bs, 4H), 6.83-8.54 (m, 15H). MS m/e 527 $(M+H)^+$.

Example 165

4-[N-Benzyl-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

A solution of triethylamine (0.51 g, 0.005 mol) and N-benzyl-N-(3-phenoxybenzyl)amine (1.45 g, 0.005 mol) in THF (30 mL) was added dropwise to a stirred solution of 1.05 g (0.005 mol) of 4-chloroformylphthalic anhydride, prepared by the method described in J. Org. Chem. 38: 2257 (1973), in THF (30 mL) at 0 °C. After the addition was complete, the reaction mixture was slowly allowed to come to ambient temperature overnight. It was then concentrated in vacuo at 20 °C. The residue obtained was treated with methylene chloride (10 mL) and 6 N HCl (90 mL) and stirred at ambient temperature for 2 hours. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed successively with 5% HCl, cold water and saturated sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure to give a viscous liquid. Chromatography on silica gel eluting with 84.5:13.5:2 $CHCl_3$-MeOH-HOAc afforded the product as a mono-methyl ester. The ester was hydrolyzed by refluxing overnight with lithium hydroxide (1.8 g, 0.043 mol) in THF (20 mL) and water (12 mL). The mixture was evaporated to remove the THF, diluted with cold water (20 mL), acidified with dilute HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with cold water and saturated sodium chloride solution, dried over sodium sulfate, evaporated and chromatographed on silica gel eluting with 95:2.5:2.5 ethyl acetate-acetic acid-water to give 1.6 g (65%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 1H), 4.30 (d, 2H), 4.7 (d, 2H), 6.7-7.85 (m, 17H), 9.5 (s, 2H). MS (DCI/NH_3) m/e 499 $(M+NH_4)^+$.

Example 166

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2-dicarboxylic acid

The title compound was prepared by treating 1.5 g (0.005 mol) of N-benzyl-N-(4-phenoxybenzyl)amine and 0.51 g (0.005 mol) of triethylamine in 30 mL of THF with 1.05 g (0.005 mol) of 4-chloroformyl phthalic anhydride in THF (20 mL) by the method described for Example 165. The crude compound

was chromatographed on silica gel eluting with 95:2.5:2.5 ethyl acetate-acetic acid-water to give 1.5 g (61%) of the title compound as a cream colored amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (d, 1H), 2.25 (q, 1H), 2.35 (s, 1H), 2.5 (t, 1H), 4-5 (m, 7H), 6.9-7.8 (m, 17H). MS (DCI/NH_3) m/e 496 $(M+H)^+$, 513 $(M+H+NH_3)^+$.

Example 167

5-[N-(1,2,3,4-Tetrahydronaphth-1-yl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 167A

N-(4-Phenoxybenzyl)-N-(1,2,3,4-tetrahydronaphth-1-yl)amine

A solution of 4-phenoxybenzaldehyde (13.5 g, 0.068 mol) and (1,2,3,4-tetrahydronaphth-1-yl)amine (10.02 g, 0.068 mol) in absolute ethanol (150 mL) containing a few crystals of p-toluenesulfonic acid was refluxed. After 4 hours, the reaction mixture was cooled, and $NaBH_4$ (2.6 g, 0.068 mol) was added portionwise over 15-20 minutes. The mixture was then heated at reflux for an additional 4 hours. The volatiles were removed under reduced pressure, and the residue was triturated with ice-water (200 mL) and extracted with ethyl acetate (4 x 80 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by column chromatography eluting with 92:8:1 hexane-ethyl acetate-triethylamine to give 17.03 g (76%) of the title compound as a colorless viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8-6.8 (m, 13H), 3.92 (d, 1H), 3.82 (t, 2H), 2.8 (m, 2H), 1.95 (m, 3H), 1.75 (m, 1H), 1.4 (s, 1H). MS (DCI/NH_3) m/e 330 $(M+H)^+$. Anal calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 84.02; H, 7.11; N, 4.28.

Example 167B

5-[N-(1,2,3,4-Tetrahydronaphth-1-yl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

A solution of N-(4-phenoxybenzyl)-N-(1,2,3,4-tetrahydronaphth-1-yl)amine (0.99 g, 0.003 mol) in anhydrous THF (40 mL) was added dropwise,

under a nitrogen atmosphere, to a stirred solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.76 g, 0.003 mol) in THF (80 mL) containing triethylamine (0.31 g, 0.003 mol) at -30 °C. After 2 hours, the cooling bath was removed. After 1.6 hours at ambient temperature, the solvent was removed under reduced pressure at 20 °C. The residue was taken up in ethyl acetate, washed with 10% HCl (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was taken up in 80 mL of THF, stirred for 1 hour with saturated sodium carbonate solution (20-30 mL) and stirred an additional hour at ambient temperature. The THF was removed under reduced pressure, and the residue was diluted with cold water (50 mL), cooled and acidified with 10% HCl. The desired product was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified by column chromatography eluting with 95:1.25:1.25:2.5 ethyl acetate-formic acid-water-methanol followed by 180:1:1 ethyl acetate-formic acid-water to give the title compound (0.5 g, 30%) as a white amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.9-6.7 (nm 15H), 5.6 (s, 1H), 4.95 (d, 1H), 4.7 (d, 2H), 4.7 (m, 1H), 3.5 (s, 2H), 2.62 (d, 1H), 2.5 (s, 1H), 2.0 (s, 1H), 1.7 (s, 1H), 1.25 (s, 1H). MS (FAB$^+$) m/e 566 $(M+H)^+$ and (FAB$^-$) 564. Anal calcd for $C_{33}H_{27}NO_8$: C, 70.08; H, 4.80; N, 2.48. Found: C, 69.90; H, 4.83; N, 2.23.

Example 168

5-[N-(1-Phenyl-2-(4-phenoxyphenyl)ethyl)aminocarbonyl]benzene-1,3-dicarboxylic acid

A mixture of 4-phenoxyphenyl benzyl ketone (5.5 g, 0.019 mol) and benzylamine (2.04 g, 0.019 mol) in methanol (250 mL) was shaken with 5% platinum on carbon (1.1 g) for 16 hours and then for 24 hours with hydrogen at 4 atmospheres. The reaction mixture was filtered, evaporated under reduced pressure and then under high vacuum to give 2-(4-phenoxyphenyl)-1-phenyl-1-aminoethane (7.0 g, 97%) as a colorless solid.

A solution of the above amine (0.54 g, 0.0014 mol) and triethylamine (0.19 mL, 0.0014 mol) in anhydrous methylene chloride was stirred at ambient

temperature while a solution of dimethyl-5-carbonyl chloride-1,3-benzene dicarboxylate (0.33 g, 0.0013 mol), prepared by the method described in Photochemistry and Photobiology 51: 155 (1990), in methylene chloride (15 mL) was added dropwise under a nitrogen atmosphere. After stirring overnight at ambient temperature, the mixture was evaporated under reduced pressure at 20 °C. The solid residue was chromatographed on silica gel eluting with 8:2 hexane-ethyl acetate to give 442 mg (57%) of 1-benzyl-1-(4-phenoxyphenyl)-1-(3,5-dimethoxycarbonyl-1-benzamido)methane.

The above diester (0.36 g, 0.0006 mol) was refluxed overnight with lithium hydroxide (0.198 g, 0.0048 mol) in a mixture of methanol (9 mL) and water (7 mL). The reaction mixture was cooled, diluted with cold water, acidified with HCl and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated under reduced pressure togive the title compound as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.40 (d, 2H), 4.75 (d, 1H), 6.78-7.4 (m, 17H), 8.4 (s, 2H), 8.85 (s, 1H). MS (DCI/NH_3) m/e 482 $(M+H)^+$, 499 $(M+H+NH_3)^+$.

Example 169

5-[N-(1,2,3,4-Tetrahydronaphth-1-yl)-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 169A

N-(1,2,3,4-Tetrahydronaphth-1-yl)-N-(3-phenoxybenzyl)amine

A solution of 3-phenoxybenzaldehyde (13.5 g, 0.068 mol) and 1,2,3,4-tetrahydronaphth-1-ylamine (10.02 g, 0.068 mol) in absolute ethanol (150 mL) containing a few crystals of p-toluenesulfonic acid was refluxed. After 4 hours, the reaction mixture was cooled and NaBH4 (2.6 g, 0.068 mol) was added portionwise over 20 minutes with stirring. The reaction mixture was again brought to reflux for an additional 4 hours and then concentrated under reduced pressure. The residue obtained was treated with ice-water (200 mL) and extracted with ethyl acetate (4 x 80 mL). The combined organic extracts were washed wtih brine (3 x 50 mL), dried over magnesium sulfate, filtered and

evaporated *in vacuo*. The residue was purified by column chromatography eluting with 92:8:1 hexane-ethyl acetate-triethylamine to give 8.0 g (36%) of the title compound as a light yellow viscous liquid. MS (DCI/NH_3) m/e 330 $(M+H)^+$. Anal calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.94; H, 7.08; N, 4.19.

Example 169B

5-[N-(1,2,3,4-Tetrahydronaphth-1-yl)-N-(3-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

A solution of the compound resulting from Example 169A (0.99 g, 0.003 mol) in anhydrous THF (40 mL) was added dropwise over two hours under a nitrogen atmosphere to a stirred solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.76 g, 0.003 mol) in THF (80 mL) containing triethylamine (0.31 g, 0.003 mol) at a temperature of from about -30 °C to about -35 °C. The cooling bath was then removed. After 2 hours at ambient temperature, the solvent was removed under reduced pressure at 20 °C. The residue was taken up in ethyl acetate, washed successively with 10% HCl (2 x 25 mL) and brine (2 x 25 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The residue was stirred at ambient temperature with a saturated sodium carbonate solution (20-30 mL) and THF (80 mL). After 1 hour, the THF was removed under reduced pressure, and the residue was diluted with cold water (30-40 mL) and acidified with 10% HCl. This mixture was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 180:1:1 ethyl acetate-formic acid-water followed by 1800:1:1 ethyl acetate-formic acid-water to give the title compound (0.4 g, 24%). ^1H NMR (DMSO-d_6, 500 MHz) δ 8.45-6.55 (m, 15H0), 5.52 (s, 1H), 4.8 (d, 1H), 4.65 (s, 1H), 4.1 (m, 1H), 3.9 (d, 2H), 2.6 (m, 2H), 2.5 (s, 1H), 2.05 (s, 1H), 1.7 (d, 1H), 1.4 (s, 1H). MS (FAB^+) m/e 566 $(M+H)^+$ and (FAB^-) m/e 564 $(M-H)^-$. Anal calcd for $C_{33}H_{27}NO_8 \cdot 0.75\ H_2O$: C, 68.44; H, 4.96; N, 2.41. Found: C, 68.36; H, 5.08; N, 2.13.

Example 170
5-[N-(4-Chromanyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 170A
N-(4-Chromanyl)-N-(4-phenoxybenzyl)amine Hydrochloride

A mixture of crude 4-amino chromane (2.9 g, 0.02 mol), prepared by reducing 4-chromanone oxime with Raney nickel in ethanol at 4 atmospheres of hydrogen for 51 hours at ambient temperature, and 4-phenoxybenzaldehyde (3.9 g, 0.02 mol) in absolute ethanol (50 mL) containing p-toluenesulfonic acid (0.1 g) was refluxed for 4 hours. The reaction mixture was then allowed to cool to ambient temperature and then treated portionwise with NaBH4 (0.8 g, 0.021 mol) with stirring. After the addition was complete, the mixture was refluxed for an additional 5 hours, cooled to ambient temperature and evaporated under reduced pressure. The residue was taken up in ethyl acetate and washed with 2 N NaOH solution (2 x 40 mL) and brine (3 x 40 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in absolute ethanol, stirred with norite, filtered, cool, and acidified with concentrated HCl. The colorless solid obtained was recrystallized from absolute ethanol to give 3.6 g (50%) of the title compound. m.p. 180-182 °C. MS (DCI/NH_3) m/e 332 $(M+H)^+$. Anal calcd for $C_{22}H_{21}NO_2 \cdot HCl$: C, 71.83; H, 6.03; N, 3.81. Found: C, 72.00; H, 5.96; N, 3.66.

Example 170B
5-[N-(4-Chromanyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

A suspension of the compound resulting from Example 170A (1.13 g, 0.003 mol) in anhydrous THF (60 mL) was added portionwise under a nitrogen atmosphere to a stirred solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.76 g, 0.003 mol) in anhydrous THF (60 mL) containing triethylamine (0.63 g, 0.006 mol) at -30 °C to -40 °C over approximately 2 hours. The cooling bath was removed, and after stirring for 3 hours at ambient temperature, the THF was removed under reduced pressure at 20 °C. The residue was taken up in ethyl

acetate, washed wtih 10% HCl and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was diluted with cold water (30-40 mL), cooled, acidified with 10% HCl and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue obtained was purified by chromatography eluting with 180:1:1 ethyl acetate-formic acid-water to give the title compound (1.26 g, 74%) as a colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.4-6.74 (m, 15H), 5.68 (s, 1H), 4.9 (q, 1H), 4.2 (m, 1H), 4.0 (q, 2H), 3.9 (d, 1H), 2.5 (s, 1H), 2.0 (s, 2H), 1.2 (t, 1H). MS (FAB$^+$) m/e 568 $(M+H)^+$ and MS (FAB$^-$) m/e566 $(M-H)^+$. Anal calcd for $C_{32}H_{25}NO_5$: C, 67.72; H, 4.44; N, 2.47. Found: C, 67.68; H, 4.76; N, 2.35.

Example 171

5-[N-(2-(Indol-3-yl)ethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

Example 171A

5-[N-(2-(Indol-3-yl)ethyl)-N-(4-phenoxybenzyl)amine

A mixture of 3-(2-aminoethyl)indole (5.8 g, 0.036 mol) and p-phenoxybenzaldehyde (6.0 g, 0.03 mol) in ethanol (250 mL) containing anhydrous 10% palladium on carbon (1.2 g) was shaken for 7 hours without hydrogen and then for 24 hours under 4 atmospheres of hydrogen. The reaction mixture was then filtered, and the filtrate concentrated *in vacuo*. The residue obtained was purified, first by recrystallization from hexane and then by chromatography eluting with 1:9:1 hexane-ethyl acetate-triethylamine to give the title compound as a white crystalline solid (5.5 g, 53%). m.p. 100-102 °C. MS (DCI/NH_3) m/e 343 $(M+H)^+$. Anal calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.67; H, 6.36; N, 8.13.

Example 171B

5-[N-(2-(Indol-3-yl)ethyl)-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

A solution of the compound resulting from Example 171A (0.7 g, 0.002 mol) in anhydrous THF (40 mL) was added dropwise under a nitrogen atmosphere to a stirred solution of 1,2,4,5-benzenetetracarboxylic dianhydride (0.51 g, 0.002 mol) in anhydrous THF (60 mL) containing N-methyl morpholine (0.21 g, 0.002 mol) cooled in a dry ice/acetone bath (-70 °C). After the addition was complete (approximately 2 hours), the cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 2 hours. The volatiles were removed under reduced pressure, and the yellow residue was dissolved in ethyl acetate. The solution was washed with 10% cold HCl and cold brine, filtered, dried and evaporated. The residue was stirred at ambient temperature with THF (60 mL) and saturated sodium carbonate solution (15 mL) for 1 hour, and then the THF was removed under reduced pressure. The residue was diluted with water, cooled in an ice bath, acidified with HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 20:1:5 chloroform-acetic acid-methanol to give the title compound (0.75 g, 68%) as a cream colored solid. MS (DCI/NH_3) m/e 577 $(M+H)^+$. ^1H NMR (DMSO-d_6, 500 MHz) δ 10.82 (s, 1H), 10.7 (s, 1H), 8.58 (s, 1H), 8.5 (s, 1H), 7.6 (d, 1H), 7.4-6.7 (m, 14H), 4.9 (s, 1H), 4.7 (s, 1H), 4.75 (s, 1H), 3.45 (s, 2H), 3.0 (s, 1H), 2.5 (s, 1H).

Example 172

4-[3-Benzyl-4-(4-phenoxyphenyl)pyrazol-2-yl]benzene-1,2-dicarboxylic acid

Example 172A

1-(4-Phenoxy)phenyl-3-phenylprop-1-yl alcohol

To a mixture of magnesium (292 mg, 12 mmol) and a small crystal of iodine in THF (5 mL) was added 1 mL of 2-phenylethyl bromide (2.04 g in 10 mL THF, 11 mmol). The mixture was gently heated with a heat gun until the reaction started (iodine color disappeared). The rest of phenylethyl bromide was added to the reaction over 20 minutes, and the reaction mixture was then heated at 50 °C for 1 hour, diluted with THF (15 mL), and cooled to 0 °C. To this mixture was added 4-phenoxybenzaldehyde (1.98 g, 10 mmol) over 10 minutes. After 1 hour at 0 °C, saturated ammonium chloride (5 mL) was added. The reaction mixture was diluted with ether (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 15% ethyl acetate in hexane to give the title compound (2.61g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 6H), 7.20 (m, 3H), 7.12 (tt, 1H), 7.01 (m, 4H), 4.68 (m, 1H), 2.70 (m, 2H), 2.10 (m, 12H), 1.90 (d, 1H).

Example 172B

4-Phenoxyphenyl 2-phenylethyl ketone

A mixture of the alcohol resulting from Example 172A (2.61 g, 8.58 mmol), pyridinium chlorochromate (2.78 g, 12.9 mmol) and activated molecular sieves (4 Å) powder (3 g) in dichloromethane (50 mL) was stirred at 0 °C for 2 hours. The mixture was then diluted with ether to 100 mL, filtered through silica gel (50 g), and rinsed with ether. Evaporation of the filtrate *in vacuo* afforded the title compound in good purity (2.43 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dt, 2H), 7.39 (tt, 2H), 7.25 (m, 6H), 7.07 (dq, 2H), 6.99 (dt, 2H), 3.28 (t, 2H), 3.06 (t, 2H).

Example 172C

Trimethylsilyl enol ether of 4-Phenoxyphenyl 2-phenylethyl ketone

To a solution of the ketone resulting from Example 172B (302.3 mg, 1.0 mmol) in THF (5 mL) at -78 °C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 1.2 mL). After 30 minutes, trimethylsilyl chloride (0.127 mL, 1.5 mmol) was added to the reaction. The cooling bath was removed, and the reaction was warmed to room temperature over 30 minutes. The reaction mixture was then poured into saturated sodium bicarbonate solution (10 mL), and extracted with ether (80 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound in good purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dt, 2H), 7.30 (m, 6H), 7.20 (m, 1H), 7.11 (tt, 1H), 7.01 (dt, 2H), 6.94 (dt, 2H), 5.36 (t, 1H), 3.55 (d, 2H).

Example 172D

1,2-Dimethoxycarbonyl-4-(1-hydroxy-3-phenyl-2-(4-phenoxybenzoyl)benzene

To a solution of the trimethylsilyl enol ether resulting from Example 172C (1.0 mmol) and 3,4-dimethoxycarbonylbenzaldehyde (222 mg, 1.0 mmol) in dichloromethane (6 mL) at -78 °C was added titanium tetrachloride (1.0 M in dichloromethane, 1.1 mL) over 10 minutes. After 5 hours, the reaction was poured into a mixture of ether (80 mL) and ice (10 g), and separated. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (353 mg, 67%) as a 1:1 mixture of 2 diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-6.80 (m, 17H), 5.17,4.97 (2 m's, 1H), 4.21,3.80 (2 d's, 1H), 3.97 (m, 1H), 3.93-3.86 (4 s's, 6H), 3.20-3.85 (4 d's, 2H).

Example 172E

1,2-Dimethoxycarbonyl-4-(1-oxo-3-phenyl-2-(4-phenoxybenzoyl)benzene

The procedure decribed in Example 172B was used to oxidize the alcohol resulting from Example 172D (251 mg, 0.48 mmol) to give the title compound (223 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 1H), 7.98 (dd, 1H), 7.83 (dt, 2H), 7.67 (d, 1H), 7.39 (m, 2H), 7.20 (m, 6H), 7.04 (dq, 2H), 6.93 (dt, 2H), 5.41 (t, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.43 (dq, 2H).

Example 172F

4-[3-Benzyl-4-(4-phenoxyphenyl)pyrazol-2-yl]benzene-1,2-dicarboxylic acid dimethyl ester

A solution of the dione resulting from Example 172E (137 mg, 0.262 mmol), anhydrous hydrazine (39 mg, 1.31 mmol) and p-tolunesulfonic acid monohydrate (50 mg) in ethanol (5 mL) was stirred at room temperature for 60 hours. The residue after concentration of the filtrate was purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (122 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (t, 1H), 7.68 (s, 2H), 7.42-7.24 (m, 6H), 7.17 (m, 4H), 7.02 (m, 4H), 4.09 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H).

Example 172G

4-[3-Benzyl-4-(4-phenoxyphenyl)pyrazol-2-yl]benzene-1,2-dicarboxylic acid

The compound resulting from Example 172F (115 mg) was stirred with saturated aqueous lithium hydroxide (0.5 mL) and methanol (3 mL) at 60 °C for 15 hours. The volatiles were removed by evaporation, and the residue was treated with aqueous 3 N HCl (2 mL). The mixture was cooled to 0 °C for 10 minutes, and the precipitate was collected by suction filtration. The solid was then dissolved in boiling ethanol (2 mL) and treated with hot water (0.5 mL). The mixture was then gradually cooled to 0 °C, and the white crystalline powder was collected by suction filtration, rinsed with cold 70% ethanol in water, and air dried to give the title compound (103 mg, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.68 (t, 2H), 7.52 (d, 2H), 7.40 (t, 2H), 7.23 (t,

3H), 7.15 (q, 2H), 7.07 (d, 2H), 7.02 (m, 4H), 4.13 (s, 2H). MS (FAB+) m/e 491 $(M+H)^+$.

Example 173

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 173A

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester (i) and

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-methanesulfonyloxypropyl]benzene-1,2-dicarboxylic acid dimethyl ester (ii)

To a 0 °C solution of the diastereomeric mixture of the hydroxyketones resulting from Example 172D (1.07 g, 2.04 mmol) in THF (30 mL) was added triethylamine (0.57 mL, 4.08 mmol), followed by methanesulfonyl chloride (0.189 mL, 2.45 mmol). The reaction was then stirred at room temperature for 2 hours and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.46 mL, 3.06 mmol). The reaction was then stirred at room temperature for 18 hours. The reaction mixture was diluted with hexane (20 mL), and to it was added anhydrous 4 N HCl in 1,4-dioxane (1 mL). The mixture was then filtered through silica gel (30 g), and rinsed with ether. The residue after evaporation of the volatiles was purified by column chromatography eluting sequentially with 20% and 35% ethyl acetate in hexane to give 173i as the first fraction (382 mg, 37%), and 173ii as the second fraction (3:1 mixture of two diastereomers, 736 mg, 60%). ^{1}H NMR for 173i (500 MHz, $CDCl_3$) δ 7.82 (dt, 2H), 7.75 (d, 1H), 7.72 9d, 1H), 7.55 (dd, 2H), 7.41 (t, 2H), 7.27 (t, 2H), 7.21 (m, 6H), 7.10 9d, 1H), 7.02 (dt, 2H), 4.09 (s, 2H), 3.93 9s, 3H), 3.92 (s, 3H). ^{1}H NMR for 173ii (the major diasteromer) (300 MHz, $CDCl_3$) δ 7.89 (d, 1H), 7.78 (d, 1H), 7.67 (dt, 2H), 7.38 (m, 2H), 7.24-7.00 (m, 7H), 6.85 (m, 4H), 5.88 (d, 1H), 4.21 (m, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 2.86 (dd, 1H), 2.77 (s, 3H), 2.47 (dd, 1H).

Example 173B

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The enone resulting from Example 173A(i) (84 mg) was stirred with saturated aqueous lithium hydroxide (0.5 mL) and methanol (3 mL) at 60 °C for 15 hours. The reaction mixture was then acidified with aqueous 3 N HCl (2 mL), diluted with ethyl acetate (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 95:5:0.5 ethyl acetate-methanol-formic acid to give the title compound (84 mg, 100%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (m, 3H), 7.66 (d, 1H), 7.45 (m, 2H), 7.30-6.80 (m, 12H), 4.02 (s, 2H). MS (FAB$^-$): m/e 477 (M-H)$^-$.

Example 174

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 174A

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester

To a solution of the methanesulfonate resulting from Example 173A (ii) (736 mg) in THF (15 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 mL). The reaction was stirred at 60 °C for 70 minutes and then diluted with hexane (10 mL) and filtered through silica gel (10 g) rinsing with ether. The residue after evaporation of the filtrate was carefully purified by column chromatography eluting with 15% ethyl acetate in hexane to give 173A(ii) as the first fraction (102 mg, 9.8% yield combined 2 steps), a fraction of mixture of compound 173A(ii) and 174A (65 mg, 6.2%), and 174A as the last fraction (364 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dt, 2H), 7.65 (d, 1H), 7.59 (dd, 1H), 7.37 (m, 8H), 7.19 (tt, 1H), 7.10 (s, 1H), 7.09 (dt, 2H), 7.02 (dt, 2H), 4.17 (s, 2H), 3.88 (s, 6H).

Example 174B

4-[3-Phenyl-2-(4-phenoxybenzoyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the enone resulting from Example 174A (42 mg) to the title compound (41 mg, 100%). ^{1}H NMR (500 MHz, DMSO-d6): δ 7.87 (dt, 1H), 7.70 (m, 1H), 7.56 (dd, 1H), 7.42 (m, 5H), 7.26 (m, 3H), 7.10 (m, 3H), 7.00 (m, 1H), 6.92 (m, 1H), 6.84 (m, 1H), 4.12 (s, 2H). MS (FAB$^-$): m/e 477 (M-H)$^-$.

Example 175

trans-4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 175A

4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester

To a solution of the enone resulting from Example 173A(i) (62.3 mg, 0.123 mmol) in methanol (3 mL) was added cerium trichloride (36.5 mg, 0.148 mmol) followed by sodium borohydride (6 mg, 0.15 mmol). After 5 minutes, saturated ammonium chloride (1 mL) was added to the reaction mixture. The reaction mixture was diluted with ether (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (63 mg) in good purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 1H), 7.63 (d, 1H), 7.47 (dd, 1H), 7.40-7.20 (m, 7H), 7.12 (m, 4H), 7.00 (m, 4H), 5.18 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (d, 1H), 3.23 (d, 1H), 1.92 (d, 1H).

Example 175B

trans-4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the enone resulting from Example 175A (58 mg) to the title compound (56 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.5 (very br s, 2H), 7.66 (d, 1H), 7.61 (s, 1H), 7.45 (d, 1H), 7.36 (m ,4H), 7.23 (t, 2H), 7.10 (m, 4H), 6.95 (t, 4H), 5.73 (s, 1H), 5.08 (s, 1H), 3.75 (d, 1H), 3.17 (d, 1H). MS (FAB$^-$) m/e 479 $(M-H)^-$.

Example 176

cis-4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 176A

cis-4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester

The procedure described in Example 175A was used to convert the enone resulting from Example 174A (115 mg) to the title compound (115 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.44 (dd, 1H), 7.38-7.20 (m, 10H, 7.13 (m, 2H), 6.99 (m, 3H), 6.96 (d, 1H), 5.16 (m, 1H), 3.89 (s, 6H), 3.86 (d, 1H), 3.38 (d, 1H), 1.93 (d, 1H).

Example 176B

cis-4-[3-Hydroxy-2-benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the enone resulting from Example 176A (48 mg) to the title compound (45 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40-7.20 (m, 12H), 7.13 (m, 1H), 6.92 (m, 4H), 5.71 (s, 1H), 5. 09 (s, 1H), 3.75 (d, 1H), 3.40 (d, 1H). MS (FAB$^-$) m/e 479 $(M-H)^-$.

Example 177
trans-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 177A
trans-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester

The compound resulting from Example 175A (180 mg, 0.352 mmol) was stirred with triethylsilane (0.4 mL) and trifluoroacetic acid (2 mL) at 70 °C for 8 hours. The reaction mixture was then concentrated *in vacuo*, and the residue was purified by column chromatography eluting with 15% ethyl acetate in hexane to give the title compound (161 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H), 7.57 (d, 1H), 7.43 (dd, 1H), 7.30 (m, 5H), 7.12 (m, 5H), 7.01 (dq, 2H), 6.95 (dt, 2H), 6.51 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.55 (s, 2H), 3.38 (s, 2H).

Example 177B
trans-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the olefin resulting from Example 177A (61 mg) to the title compound (60 mg, 100%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, 1H), 7.83 (s, 1H), 7.44 (dd, 1H), 7.38 (t, 2H), 7.30 (t, 2H), 7.21 (m, 3H), 7.14 (m, 3H), 6.97 (m, 4H), 6.63 (s, 1H), 3.52 (s, 2H), 3.35 (s, 2H). MS (FAB$^-$): m/e 463 $(M-H)^-$.

Example 178

cis-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

Example 178A

cis-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid dimethyl ester

The procedure described in Example 177A was used to convert the compound resulting from Example 176A (47 mg) to the title compound (43 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H), 7.43 (dd, 1H), 7.37-7.17 (m, 6H), 7.10 (m, 4H), 7.01 (m, 2H), 6.93 (m, 3H), 6.64 (s, 1H), 3.91 (s, 6H), 3.61 (s, 2H), 3.35 (s, 2H).

Example 178B

cis-4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propenyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the olefin resulting from Example 178A (40 mg) to the title compound (37 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 7.54 (s, 1H), 7.38-7.10 (m, 11H), 6.96 (m, 4H), 6.67 (s, 1H), 3.59 (s, 2H), 3.37 (s, 2H). MS (FAB$^-$) m/e 463 (M-H)$^-$.

Example 179

4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propyl]benzene-1,2-dicarboxylic acid

Example 179A

4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propyl]benzene-1,2-dicarboxylic acid dimethyl ester

A mixture of the olefin resulting from Example 177A (107 mg) and 10% palladium on carbon (100 mg) in ethanol (2 mL) and ethyl acetate (2 mL) was stirred under a hydrogen balloon for 5.5 hours. The reaction mixture was then diluted with ether (20 mL), filtered through silica gel (5 g) and rinsed with ether. Concentration of the filtrate afforded the title compound (105 mg, 99%) in good purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H), 7.41 (d, 1H), 7.35-7.14 (m, 5H), 7.11-7.02 (m, 6H), 6.98 (m, 2H), 6.92 (dt, 2H), 3.91 9s, 3H), 3.89 (s, 3H), 2.64-2.44 (m, 6H), 2.30 (m, 1H).

Example 179B

4-[2-Benzyl-3-(4-phenoxyphenyl)-1-propyl]benzene-1,2-dicarboxylic acid

The procedure described in Example 173B was used to convert the compound resulting from Example 179A (83 mg) to the title compound (54 mg, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (br s, 1H), 7.76 (br s, 1H), 7.37 (m, 2H), 7.28 (m, 2H), 7.14 (m,m 7H), 6.97 (dt, 2H), 6.90 (dt, 2H), 2.58 (d, 2H), 2.50 (m, 4H), 2.14 (m, 1H). MS (FAB$^-$) m/e 465 (M-H)$^-$.

Example 180

6-Vinyl-3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,4-dicarboxylic acid

Example 180A

3,6-Di[trifluoromethanesulfonyloxy]benzene-1,4-dicarboxylic acid diethyl ester

To a 0 °C solution of diethyl 2,5-dihydroxyterephthalate (4.24 g, 16.7 mmol) and pyridine (8 mL) in dichloromethane (30 mL) was slowly added trifluoromethanesulfonic anhydride (5.9 mL, 35 mmol). The reaction was allowed to warm to ambient temperature over 2 hours, and another portion of trifluoromethanesulfonic anhydride (1 mL, 5.7 mmol) was added. After another 1 hour, the reaction was diluted with ethyl acetate (200 mL), washed with aqueous 1 N HCl (50 mL), saturated copper (II) sulfate (50 mL), water (50 mL), and brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate, and the mother liquid was concentrated and purified by column chromatography eluting with 10% ethyl acetate in hexane to give the title compound (8.05 g combined yield, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 2H), 4.51 (q, 4H), 1.44 (t, 6H).

Example 180B

2-Trifluoromethanesulfonyloxy-5-vinylbenzene-1,4-dicarboxylic acid diethyl ester

A solution of the bistriflate resulting from Example 180A (5.19 g, 10.0 mmol), vinyltributyltin (3.17 g, 10.0 mmol), bis(triphenylphosphine)palladium dichloride (210 mg, 0.3 mmol), and anhydrouse lithium chloride (1.3 g, 30 mmol) in anhydrous 1,4-dioxane (30 mL) was degassed by bubbling nitrogen through the solution for 5 minutes. The mixture was then heated at 85 °C for 6 hours. After the reaction mixture was cooled to room temperature, it was filtered through silica gel (30 g), and the filtrate was diluted with ether to 100 mL. To the filtrate was added water (0.5 mL), followed by the dropwise addition of DBU (3 mL) with good stirring. The mixture was immediately filtered through silica gel (50 g), rinsed with ether several times, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 5% followed by 10% ether in hexane to give the title compound (3.73 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.78 (s, 1H), 7.44 (dd, 1H), 5.78 (dd, 1H), 5.50 (dd, 1H), 4.48 (q, 2H), 4.41 (q, 2H), 1.44 (t, 3H), 1.42 (t, 3H).

Example 180C

2,5-Diethoxycarbonyl-4-trifluoromethanesulfonyloxybenzoic acid

A mixture of the olefin resulting from Example 180B (711 mg, 1.79 mmol), sodium periodate (1.96 g, 9.0 mmol) and ruthenium trichloride monohydrate (11 mg, 0.05 mmol) in a mixed solvent system of carbon tetrachloride (4 mL), acetonitrile (4 mL) and water 96 mL) was well stirred at 60 °C for 4 hours. After allowing to cool to ambient temperature, the reaction mixture was diluted with ethyl acetate (100 mL), washed with 0.1 N HCl, water and brine, dried over anhydrous magnesium sulfate, filtered through silica gel (20 g), washed with 5% methanol in ethyl acetate, and concentrated *in vacuo* to give the title compound which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 9s, 1H), 7.62 (s, 1H), 4.47 (m, 4H), 1.44 (t, 3H), 1.38 (t, 3H).

Example 180D

1,4-Diethoxycarbonyl-2-trifluoromethanesulfonyloxy-5-[N-benzyl-N-4-(phenoxybenyl)aminocarbonyl]benzene

To a suspension of the acid resulting from Example 180C in dichloromethane (5 mL) was added oxalyl chloride (2.0 M in dichloromethane, 1. 8 mL), followed by the addition of a tiny drop of N,N-dimethylformamide. After the mixture was stirred 2 hours at room temperature, the solvent was evaporated, and the residue was further dried under high vacuum for 10 minutes. The acid chloride was redissolved in dichloromethane (5 mL), and N-benzyl-N-(4-phenoxy)benzylamine (625 mg, 2.16 mmol) was added to the reaction mixture. After 30 minutes, the reaction mixture was filtered through silica gel (10 g), and then rinsed with ethyl acetate. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with 20% ethyl acetate in hexane to give the title compound (1.01 g, 82% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98,7.96 (2 s's, 1H), 7.90,7.88 (2 s's, 1H), 7.42-7.28 (m, 8H), 7.15-7.95 (m, 6H), 4.79,4.76 (2 s's, 2H), 4.47-4.30 (4 q's, 4H), 4.24,4.20 (2 s's, 2H), 1.43-1.25 (4 t's, 6H).

Example 180E

1,4-Diethoxycarbonyl-6-vinyl-3-[N-benzyl-N-4-(phenoxybenyl)aminocarbonyl]benzene

The method described in Example 180B was used to convert the olefin resulting from Example 180D (945 mg, 1.38 mmol) to the title compound (724 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21,8.18 (2 s's, 1H), 7.87,7.865 (2s's, 1H), 7.50-7.28 (m, 9H), 7.16-7.96 (m, 6H), 5.79,5.73 (2 dd's, 1H), 5.48,5.44 (2 dd's, 1H), 4.77,4.72 (2 br s's, 2H), 4.40-4.30 (4 q's, 4H), 4.26,4.22 (2 s's, 2H), 1.40-1.23 (4 t's, 6H).

Example 180F

6-Vinyl-3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]benzene-1,4-dicarboxylic acid

The procedure described in Example 173B was used to convert the compound resulting from Example 180E (31 mg) to the title compound (7.5 mg, 28%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.30,8.29 (2 s's, 1H), 7.76,7.74 (2s's, 1H), 7.57-7.24 (m, 9H), 7.16-7.93 (m, 6H), 5.82 (d, 1H), 5.42 (dd, 1H), 4.85-4.76 (2H), 4.30,4.28 (2 s's, 2H). MS (FAB$^+$) m/e 508 $(M+H)^+$.

Example 181

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-3-hydroxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

Example 181A

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-6-formyl-benzene-1,4-dicarboxylic acid diethyl ester

A mixture of the olefin resulting from Example 180E (714 mg, 1.27 mmol), sodium periodate (0.66 M in water, 5.8 mL, 3.81 mL), and osmium tetraoxide (0.08 M in tert-butanol, 0.32 mL, 0.025 mmol) in 1,4-dioxane (20 mL) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ether (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (691 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62,10.61 (2 s's. 1H), 8.56,8.55 (2 s's, 1H), 7.92 (s, 1H), 7.43-7.28 (m, 8H), 7.15-6.93 (m, 6H), 4.78 (br s, 2H), 4.47-4.33 (4 q's, 4H), 4.23,4.18 (2 s's, 2H), 1.43-1.32 (4 t's, 6H).

Example 181B

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-3-hydroxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

The method described in Example 173B was used to convert the adehyde resulting from Example 181A (721 mg, 1.28 mmol) to the title compound (619 mg, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31,8.30 (2 s's, 1H), 7.77,7.76 (2 s's, 1H), 7.38-7.22 (m, 8H), 7.15-6.83 (m, 6H), 6.64 (br s, 1H), 4.20 (m, 4H). MS (FAB$^+$) m/e 510 (M+H)$^+$.

Example 182

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]-3-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

A mixture of the hemiacetal resulting from Example 181B (331 mg, 0.65 mmol), anhydrous 4.0 N HCl in dioxane (0.5 mL), anhydrous 4Å molecular sieves (1 g) in methanol (3 mL) was stirred at 60 °C for 15 hours. The reaction mixture was diluted with ethyl acetate to 20 mL, filtered through celite, rinsed with ethyl acetate, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting sequentially with 100% ethyl acetate, followed by 2% and 5% methanol in ethyl acetate to give the title compound (71 mg, 21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18,8.16 (2 s's, 1H), 7.81,7.78 (2 s's, 1H), 7.42-7.24 (m, 7H), 7.17 (m, 3H),7.04-6.85 (m, 4H), 6.60,6.58 (2 s's, 1H), 4.25,4.22 (2 br s's, 4H), 3.57 (s, 3H). MS (FAB$^+$) m/e 524 (M+H)$^+$.

Example 183

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]-3-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

Example 183A

2-Trifluoromethanesulfonyloxy-5-allyl-benzene-1,4-dicarboxylic acid diethyl ester

The method used in Example 180B was used to convert the bistriflate resulting from Example 180A (1.04 g, 2.0 mmol) to the title compound (748 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.77 (s, 1H), 5.96 (m, 1H),

5.52 (dq, 1H), 5.05 9dq, 1H), 4.46 (q, 2H), 4.39 (q, 2H), 3.80 (dt, 2H), 1.43 (t, 3H), 1.40 (t, 3H).

Example 183B

2-Trifluoromethanesulfonyloxy-5-carboxymethyl-benzene-1,4-dicarboxylic acid diethyl ester

The method described in Example 180C was used to convert the olefin resulting from Example 183A (974 mg, 1.81 mmol) to the title compound (560 mg, 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.51 (s, 1H), 8.10 (s, 1H), 7.89 (s, 1H), 4.39 (q, 2H), 4.31 (q, 2H), 4.07 (s, 2H), 1.35 (t, 3H), 1.30 (t, 3H).

Example 183C

2-Trifluoromethanesulfonyloxy-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzene-1,4-dicarboxylic acid diethyl ester

The method described in Example 180D was used to convert the acid resulting from Example 183B (547 mg, 1.28 mmol) to the title compound (815 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.89 (s, 1H), 7.43-7.22 (m, 10H), 7.13 (m, 1H), 7.06-6.94 (m, 3H), 4.63,4.62,4.60,4.58 (4 s's, 4H), 4.45 (2 q's, 2H), 4.35 (2 q's, 2H), 4.25, 4.22 (2 s's, 2H), 1.42-1.32 (4 t's, 6H).

Example 183D

5-Vinyl-2-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzene-1,4-dicarboxylic acid diethyl ester

The method described in Example 180B was used to convert the compound resulting from Example 183C (808 mg, 1.16 mmol) to the title compound (605 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.73 (d, 1H), 7.47-7.23 (m, 11H), 7.11 (m, 1H), 7.05-6.93 (m, 3H), 6.75 (d, 1H), 5.39 (D, 1H), 4.62,4.60,4.57 (3 S'S, 2H), 4.41-4.38 (4 q'S, 4H), 4.20,4.17 (2 s's, 2H), 1.41-1.32 (4 t's, 6H).

Example 183E

2-Formyl-5-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzene-1,4-dicarboxylic acid diethyl ester

The method described in Example 181A was used to convert the compound resulting from Example 183D (344 mg, 0.595 mmol) to the title compound (265 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.62,10.61 (2 s's. 1H), 8.54,8.53 (2 s's, 1H), 7.83,7.81 (2 s's, 1H), 7.43-7.23 (m, 10H), 7.12 (m, 1H), 7.07-6.93 (m, 3H), 4.64,4.63,4.61,4.59 (4 s's, 4H), 4.45 (2 q's, 2H), 4.35 (2 q's, 2H), 4.30, 4.27 (2 s's, 2H), 1.45-1.35 (4 t's, 6H).

Example 183F

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]-3-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

The aldehyde resulting from Example 183E (30 mg) was stirred with saturated aqueous lithium hydroxide (0.5 mL) and methanol (3 mL) at 45 °C for 15 hours. The reaction mixture was then acidified with aqueous 3 N HCl (2 mL), stirred at room temperature for 30 minutes, diluted with ethyl acetate (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 5% methanol in ethyl acetate to give the title compound (25 mg, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11,8.10 (2 s's, 1H), 7.86,7.83 (2 s's, 1H), 7.43-7.20 (m, 10H), 7.15 (m, 1H), 7.04-6.90 (m, 3H), 6.60 (s, 1H), 4.65,4.62 (2 s's, 2H), 4.46,4.43,4.41,4.38 (4 s's, 4H), 3.58 (s, 3H). MS (FAB$^+$) m/e 538 $(M+H)^+$.

Example 184
6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

Example 184
6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid ethyl ester

To 0 °C a solution of the aldehyde resulting from Example 183E (232 mg, 0.40 mmol) in tetrahydrofuran (4 mL) and methanol (1 mL) was added sodium borohydride (38 mg, 1.0 mmol). After 20 minutes, the reaction mixture was diluted with ether (100 mL), washed with 0.1 N HCl, water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 30% ethyl acetate in hexane to give the title compound (151 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16(s, 1H), 7.85,7.81 (2 s's, 1H), 7.43-7.22 (m, 10H), 7.15 (m, 1H), 7.08-6.92 (m, 3H), 5.35 (s, 2H), 4.66,4.64,4.62,4.60 (4 s's, 4H), 4.36,4.35 (2 q's, 2H), 4.30,4.27 (2 s's, 2H), 1.35-1.34 (2 t's, 3H).

Example 184B
6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

The lactone resulting from Example 184A (141 mg, 0.26 mmol) was stirred with saturated aqueous lithium hydroxide (0.5 mL) and methanol (3 mL) at 45 °C for 15 hours. The reaction mixture was then acidified with aqueous 3 N HCl (2 mL), diluted with ethyl acetate (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then stirred with p-toluensulfonic acid (10 mg), anhydrous molecular sieves (4Å, 1 g) in toluene (5 mL) at 80 °C for 60 hours. The reaction mixture was filtered through celite, rinsed with ethyl acetate, and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 96:3:0.5 ethyl acetate-methanol-acetic acid to give the title compound (77 mg, 58%). ^{1}H NMR (500 MHz, $CDCL_3$): δ 8.02,8.00 (2 s's, 1H), 7.55,7.46 (2 s's, 1H), 7.38-7.30 (m, 10H), 7.18-6.97 (m, 2H), 6.90-6.83

(m, 2H), 5.24,5.23 (2 s's, 2H), 4.63,4.60,4.58,4.57 (4 s's, 4H), 4.17,4.10 (2 s's, 2H). MS (FAB –): m/e 506 (M–H).

Example 185

5-Hydroxymethyl-2-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonylmethyl]benzene-1,4-dicarboxylic acid disodium salt

To a solution the lactone resulting from Example 184B (42.1 mg, 0.083 mmol) in THF (3 mL) was added aqueous 2.00 M sodium hydroxide (0.249 mL). After 1 hour, the solvent was evaporated *in vacuo* to give the title compound (51.2 mg, 100%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (q, 1H), 7.68, 7.66, 7.61, 7.57 (4 s's, 1H), 7.43-7.30 (m, 11H), 7.01-6.89 (m, 3H), 5.34 (d, 2H), 4.63-4.26 (many singlets, 6H), 3.67 (dd, 2H).

Example 186

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]-3-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

Example 186A

Dimethyl 2-amino-5-bromoterephthalate

To a -40 °C solution of dimethyl aminoterephthalate (4.39 g, 21 mmol) and pyridine (2.0 mL, 23 mmol) in dichloromethane (40 mL) was added slowly bromine (1.0 M in dichloromethane, 22 mL) over 15 minutes. After 1 hour at -45 °C, the reaction was diluted with a mixture of ether and hexane (1:1, 40 mL), and was filtered through silica gel (50 g), rinsed with ether and dichloromethane (1:1), and concentrated *in vacuo*. The residue was then crystallized from ethyl acetate to give the title compound as yellowish green needles (4.23 g), and the mother liquid was concentrated *in vacuo*, and then purified by column chromatography eluting with 15% ethyl acetate in hexane to give more title compound (1.27 g, combined yield, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H)), 7.06 (s, 1H), 5.80 (br s, 2H), 3.92 (s, 3H), 3.89 (s, 3H).

Example 186B

Dimethyl 2-amino-5-vinylterephthalate

The method described in Example 180B was used to convert the bromide resulting from Example 185A (4.43 g, 15.4 mmol) to the title compound (2.74 g, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.21 (dd, 1H), 7.14 (s, 1H), 5.78 (br s, 2H), 5.55 (dd, 1H), 5.19 (dd, 1H), 3.91 (s, 3H), 3.89 (s, 3H).

Example 186C

Dimethyl 2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]-5-vinylterephthalate

A solution of the compopund resulting from Example 186B (2.72 g, 11.6 mmol) and triphosgene (1.21 g, 4.06 mmol) in THF (15 mL) was heated at 60 °C for 16 hours. After it was cooled to room temperature, N-benzyl-N-(4-phenoxy)benzylamine (4.36 g, 15.1 mmol) and triethylamine (4.9 mL, 35 mmol) were added sequentially. The reaction was then heated at 505 °C for 3 hours. The reaction mixture was filtered through silica gel (50 g), rinsed with ether, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 20% ethyl acetate in hexane to give the title compound (4.78 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.14 (s, 1H), 8.19 (s, 1H), 7.38-7.22 (m, 10H), 7.10 (tt, 1H), 6.98 (m, 4H), 5. 63 (dd, 1H), 5.31 (dd, 1H), 4.65 (br s, 2H), 4.62 (br s, 2H), 3.92 (s, 3H), 3.84 (s, 3H).

Example 186D

Dimethyl 2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]-5-formylterephthalate

The method described in example 181A was used to convert the compound resulting from Example 186C (2.61 g, 4.73 mmol) to the title compound (2.13 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.22 (s, 1H), 10.42 (s, 1H), 9.26 (s, 1H), 8.63 (s, 1H), 7.38-7.22 (m, 9H), 7.10 (tt, 1H), 6.98 (m, 4H), 4.67 (s, 2H), 4.63 (s, 2H), 3.98 (s, 3H), 3.86 (s, 3H).

Example 186E

6-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]-3-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid

The method described in Example 183F was used to convert the aldehyde resulted from Example 186D (629 mg, 1.14 mmol) to the title compound (517 mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.17 (s, 1H), 7.41-7.24 (m, 9H), 7.12 (tt, 1H), 6.98 (m, 4H), 6.50 (s, 1H), 4.61 (br s, 2H), 4.58 (br s, 2H). MS (FAB$^+$) m/e 539 (M+H)$^+$.

Example 187

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,2,4-tricarboxylic acid

Example 187A

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,2,4-tricarboxylic acid 1,4-dimethyl ester

The method described in Example 180C was used to convert the compound resulting from Example 186C (2.17 g, 3.94 mmol) to the title compound (973 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.23 (s, 1H), 8.99 (s, 1H), 8.69 (s, 1H), 7.39-7.22 (m, 9H), 7.11 (tt, 1H), 6.99 (m, 4H), 4.65 (br s, 2H), 4.61 (br s, 2H), 3.94 (s, 3H), 3.87 (s, 3H).

Example 187B

5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylamino]benzene-1,2,4-tricarboxylic acid

The method described in Example 173B was used to convert the compound resulting from Example 187A (132 mg, 0.23 mmol) to the title compound (91 mg, 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (br s, 1H), 8.43 (br s, 1H), 7.42-7.26 (m, 9H), 7.14 (tt, 1H), 6.98 (m, 4H), 4.63 (br s, 2H), 4.60 (br s, 2H). MS (FAB –): m/e 539 (M–H).

Example 188

5-[N-Benzyl-N-(4-(4-methoxyphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

To a mixture of 774 mg (19.4 mmol) of a 60% emulsion of sodium hydride in mineral oil in 3 mL of dry dimethylformamide (DMF) cooled to 0 °C, was slowly added a solution of 2.00 g (16.1 mmol) of 4-methoxyphenol in 3 mL of dry DMF. The mixture was allowed to warm to ambient temperature and was then treated with a solution of 4-fluorobenzaldehyde in 3 mL of dry DMF. After 18 hours, 30 mL of water was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed repeatedly with water, dried ($MgSO_4$), and all volatiles were removed under reduced pressure affording 3.7 g (100%) of imine as a yellow oil. This crude product was dissolved in 20 mL of ethanol, to which was added 1.72 g (16.1 mmol) of benzylamine. The solution was stirred for 6 hours under a nitrogen atmosphere and was then treated with 0.61 g (16 mmol) of sodium borohydride. After 20 hours all volatiles were removed under reduced pressure, water was added and the mixture was extracted with ethyl acetate. All volatiles were removed under reduced pressure and concentrated hydrochloric acid was added. The resulting solid was crystallized from ethanol, affording 2.76 g (54%) of the amine hydrochloride as a white solid.

A mixture of 1.06 g (3.32 mmol) of the amine and 0.724 g (3.32 mmol) of 1,2,4,5-benzenetetracarboxylic dianhydride in 600 mL of dry tetrahydrofuran (THF) was cooled to -50 °C under a nitrogen atmosphere. To this was added dropwise 1.01 g (9.97 mmol) of triethylamine in 50 mL of dry THF. The reaction mixture was allowed to slowly warm to ambient temperature. After 20 hours all volatiles were removed under reduced pressure. The product was dissolved in 40 mL of ethyl acetate, and the solution was extracted with dilute hydrochloric acid. All volatiles were removed under reduced pressure, and the resulting product was dissolved in 100 mL of THF. To this was added 20 mL of saturated sodium carbonate, and the mixture was stirred vigorously for 6 hours. The mixture was acidified with concentrated HCl, and the solution was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and all volatiles were removed under reduced pressure, affording an oil. Purification by flash column

chromatography on silica gel eluting with 180:1:1 ethyl acetate-formic acid-water afforded 110 mg (6%) of the title compound as a foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.75 (s, 3H), 4.1-4.2 (m, 2H), 4.4-4.5 (m, 2H), 6.8-7.4 (m, 15H). MS (FAB)$^-$ m/e 554 (M-H)$^-$.

Example 189

5-[N-Benzyl-N-(3-(4-methylphenoxy))benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 3-(4-methylphenoxy)benzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52 (s, 3H), 4.20 (d, J=8 Hz, 2H), 4.3-4.8 (m, 2H), 6.8-7.0 (m, 5H), 7.1-7.6 (m, 10H). MS (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 190

5-[N-Benzyl-N-(4-(4-tert-butylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 3-(4-t-butylphenoxy)benzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 9H), 4.0-4.2 (m, 4H), 6.8-7.0 (m, 5H), 7.1-7.5 (m, 10H). MS (FAB)$^-$ m/e 580 (M-H)$^-$.

Example 191

5-[N-Benzyl-N-(4-(allyloxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 4-allyloxybenzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.1-4.2 (m, 2H), 4.5-4.6 (m, 2H), 5.2-5.3 (m, 1H), 5.3-5.5 (m, 1H), 5.9-6.1 (m, 1H), 6.8-6.9 (m, 2H), 7.0-7.2 (m, 2H), 7.2-7.5 (m, 6H), 7.6-7.7 (m, 1H). MS (FAB)$^-$ m/e 488 (M-H)$^-$.

Example 192

5-[N-Benzyl-N-(4-(butoxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 4-butoxybenzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (t, J=8 Hz, 3H), 1.3-1.5 (m, 2 H), 1.6-1.8 (m, 2 H), 3.1-3.7 (m, 2 H), 3.8-4.0 (m, 2H), 4.0-4.2 (m, 2H), 6.7-7.7 (m, 11H). MS (FAB)$^-$ m/e 504 (M-H)$^-$.

Example 193

5-[N-Benzyl-N-(4-(2-methoxyphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was made from 2-methoxyphenol and 4-fluorobenzaldehyde. The amine was prepared from this aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.73 and 3.75 (2s, total = 3H) 4.0-4.6 (m, 4H), 6.7-6.8 (m, 2H), 7.0-7.4 (m, 12H), 7.6-7.7 (m, 1H). MS (FAB)$^-$ m/e 554 (M-H)$^-$.

Example 194

5-[N-Benzyl-N-(4-(4-benzyloxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 4-benzyloxybenzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.1-4.2 (m, 2H), 4.2-5.0 (m, 2H), 5.0-5.1 (m, 2H), 6.9-7.5 (m,15H). MS (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 195

5-[N-Benzyl-N-(4-(2-methylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was made from 2-methylphenol and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures d scribed in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.13

and 2.17 (2s, total = 3H) 4.1-4.2 (m, 2H), 4.2-5.8 (m, 2H), 6.7-7.4 (m, 15H). MS (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 196

5-[N-Benzyl-N-(3-methoxy-4-benzyloxybenzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding amine was prepared from 4-benzyloxy-3-methoxybenzaldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.70 and 3.78 (2s, total = 3H), 4.1-4.2 (m, 2H), 4.2-4.9 (m, 2H), 5.00 and 5.05 (2s, total = 2H), 6.6-7.4 (m,15H). MS (FAB)$^-$ m/e 568 (M-H)$^-$.

Example 197

5-[N-Benzyl-N-(3-(2-benzylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from 2-hydroxydiphenylmethane and 3-bromobenzaldehyde according to the procedure of Kodama, et. al. (Kodama, M.; Shiobara, Y.; Sumitomo, H.; Matsumura, K.; Tsakamoto, M.; Harada, C. J. Org. Chem., 53, 72-77 (1988). The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.8-3.9 (m, 2H), 4.1-4.2 (m, 2H), 4.2-4.9 (m, 2H), 6.7-7.2 (m, 20H). MS (FAB)$^-$ m/e 614 (M-H)$^-$.

Example 198

5-[N-Benzyl-N-(4-(3,4-dimethylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from3,4-dimethylphenol and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (bs, 6H) 4.1-4.2 (m, 2H), 4.4 (d, J=7Hz, 2H), 7.0-7.4 (m,14H). MS (FAB)$^-$ m/e 552 (M-H)$^-$.

Example 199

5-[N-Benzyl-N-(4-(3,4-dimethylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from 2,4,6-trimethylphenol and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.9-2.0 (m, 9H) 4.0-4.2 (m, 2H), 4.0-4.8 (m, 2H), 6.5-6.7 (m, 2H), 6.9-7.4 (m,11H). MS (FAB)$^-$ m/e 566 (M-H)$^-$.

Example 200

5-[N-Benzyl-N-(4-(3,4-dimethylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from 4-methylphenol and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H) 4.1-4.2 (m, 2H), 4.2-4.9 (m, 2H), 6.8-7.4 (m,15H). MS (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 201

5-[N-Benzyl-N-(4-(3-methylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from 3-methylphenol and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H) 4.1-4.2 (m, 2H), 4.2-5.0 (m, 2H), 6.6-7.4 (m,15H). MS (FAB)$^-$ m/e 538 (M-H)$^-$.

Example 202

5-[N-(2-Ethoxybenzyl)-N-(4-(4-benzylphenoxy)benzyl)aminocarbonyl]benzene-1,2,4-tricarboxylic acid

The corresponding aldehyde was prepared from 4-hydroxydiphenylmethane and 4-fluorobenzaldehyde. The corresponding amine was prepared from the above aldehyde and benzylamine. The title compound was prepared by the procedures described in Example 188 ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.1-1.2 (m, 3H), 3.8-5.0 (m, 8H), 6.8-7.4 (m,19H). MS (FAB)$^-$ m/e 658 $(M-H)^-$.

Example 203

4-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonylthioalkoxy]benzene-1,2-dicarboxylic acid

Example 203A

Dimethyl 4-{[N,N-dimethylaminothiocarbonyl]oxy}phthalate

Dimethyl 4-hydroxyphthalate was converted to the title compound using the method described in J. Org. Chem., 31: 3980 (1966), and purified by chromatography using 98:2 $CHCl_3$-EtOAc. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1H), 7.42 (d, 1H), 7.25 (dd, 1H), 3.91, 3.90 (both s, total 6H), 3.45 (s, 3H), 3.35 (s, 3H). MS (DCI/NH_3) m/e 298 $(M+H)^+$, 315 $(M+H+NH_3)^+$.

Example 203B

Dimethyl 4-mercaptophthalate

The compound resulting from Example 203A was heated to 230 °C under N_2 for 30 minutes to give dimethyl 4-{[N,N-dimethylaminocarbonyl]thio}-phthalate. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H), 7.71 (d, 1H), 7.67 (dd, 1H), 3.92, 3.90 (both s, total 6H), 3.07 (v. br. s, 6H). MS (DCI/NH_3) m/e 298 $(M+H)^+$, 315 $(M+H+NH_3)^+$.

The above compound was saponified by the method described in Org. Syn., Coll. Vol. VI, 825, then converted to the title compound by Fischer esterification. ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 1H), 7.50 (d, 1H), 7.37 (dd, 1H), 3.92

(s,3H), 3.88 (s, 3H), 3.64 (s, 1H). MS (DCI/NH_3) m/e 227 $(M+H)^+$, 244 $(M+H+NH_3)^+$.

Example 203C

Dimethyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]thio}phthalate

The compound resulting from Example 203B was converted to the title compound by the method of Example 38A. ^1H NMR ($CDCl_3$) δ 7.90 (m, 1H), 7.70 (m, 2H), 7.41-7.08 (envelope, 10H), 7.00 (br m, 4H), 4.57 (s, 2H), 4.51 (s, 2H), 3.92 (s, 6H). MS (DCI/NH_3) m/e 559 $(M+H+NH_3)^+$.

Example 203D

4-{[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]thio}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 203C by the method of Example 36C, except 1:1 hexane-EtOAc followed by 18:1:1 EtOAc-H_2O-CH_3CO_2H was used for the chromatography. ^1H NMR (DMSO-d_6) δ 7.80, 7.73, 7.38, 7.30, 7.15, 7.00 (all m, total 17H), 4.60 (v br s, 4H). MS (FAB-) m/e 512 $(M-H)^-$. Anal calcd for $C_{29}H_{23}NO_6S$: C, 67.82; H, 4.51; N, 2.73. Found: C, 67.50; H, 4.51; N, 2.46.

Example 204

4-{2-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]ethyl}benzene-1,2-dicarboxylic acid

Example 204A

Dimethyl 4-(diazoacetyl)methylphthalate

Dimethyl 4-carboxymethylphthalate (300 mg, 1.20 mmol) was dissolved in CH_2Cl_2 (5 mL), then oxalyl chloride (167 mg, 115 µL, 1.32 mmol) was added, followed by a drop of DMF. After stirring at room temperature for 45 minutes, the reaction was concentrated, redissolved in CH_3CN (2 mL), then added dropwise to a 0 °C mixture of CH_3CN (2 mL) and trimethylsilyldiazomethane (1.3 mL of a 2 M in hexane solution, 2.60 mmol). The reaction was stirred at

0-5 °C for 3.5 hours, concentrated, and purified by chromatography eluting with 6:4 hexane-EtOAc to give 140 mg (42%) of the title compound as a dark brown, tacky solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H), 7.59 (d, 1H), 7.44 (dd, 1H), 5.18 (s, 1H), 3.92, 3.91 (both s, total 6H), 3.68 (s, 2H). MS (DCI/NH_3) m/e 277 $(M+H)^+$, 294 $(M+H+NH_3)^+$.

Example 204B

Dimethyl 4-(2'-carbobenzoxy)ethylphthalate

The resultant compound from Example 204A (135 mg, 0.49 mmol) in THF (2 mL) and benzyl alcohol (0.25 mL) was treated with a solution of silver benzoate in triethylamine (150 µL of 66 mg AgOBn in 1.3 mL triethylamine). After 1.5 hours, the reaction was concentrated and purified by chromatography eluting with 4:1 hexane-EtOAc to give 109 mg (62%) of the title compound as a clear and colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 1H), 7.53 (d, 1H), 7.33 (m, 6H), 5.11 (s, 2H), 3.92, 3.91 (both s, total 6H), 3.04 (t, 2H), 2.70 (t , 2H). MS (DCI/NH_3) m/e 357 $(M+H)^+$, 374 $(M+H+NH_3)^+$.

Example 204C

Dimethyl 4-(2'-carboxy)ethylphthalate

The resultant compound from Example 204B (103 mg, 0.29 mmol) was dissolved in EtOAc (5 mL), then 10% Pd/C (30 mg) was added and the slurry stirred under H_2 balloon for 2.5 hours. The reaction was filtered through celite and concentrated to give 75 mg (97%) of the title compound as a white crystalline solid. ^{1}H NMR (CD_3OD) δ 7.67 (d, 1H), 7.55 (d, 1H), 7.47 (dd, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.98 (t, 2H), 2.63 (t , 2H). MS (DCI/NH_3) m/e 267 $(M+H)^+$, 284 $(M+H+NH_3)^+$.

Example 204D

Dimethyl 4-{2'-[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]ethyl}phthalate

The title compound was prepared from the compound resulting from Example 204C by the method of Example 28C. ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, 1H), 7.50 (dd, 1H), 7.33 (m, 6H), 7.20-6.92 (envelope, 9H), 4.59 (d, 2H), 4.40 (d,

2H), 3.90, 3.88 (both s, total 6H), 3.10 (m, 2H), 2.74 (m, 2H). MS (DCI/NH_3) m/e 555 $(M+H+NH_3)^+$.

Example 204E

4-{2'-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]ethyl}benzene-1,2-dicarboxylic acid

The title compound was prepared from the compound resulting from Example 204D by the method of Example 27D. ^1H NMR (DMSO-d_6) δ 7.59 (m, 1H), 7.50 (m, 1H), 7.45-7.10 (envelope, 11H), 6.97 (m, 4H), 4.50 (m, 4H), 2.97 (m, 2H), 2.78(m, 2H). MS (FAB+) m/e 510 $(M+H)^+$ and (FAB-) m/e 508 $(M-H)^-$. Anal calcd for $C_{31}H_{27}NO_6 \cdot 0.25\ H_2O$: C, 72.43; H, 5.39; N, 2.72. Found: C, 72.40; H, 5.18; N, 2.56.

Example 205

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino-6-carboxy-thiophenol

Example 205A

Methyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-hydroxybenzoate

Methyl 4-amino-2-hydroxybenzoate, prepared by treating 4-aminosalicylic acid with diazomethane, was converted to the title compound by the method of Example 34D, except no K_2CO_3 was added. ^1H NMR ($CDCl_3$) δ 10.78 (s, 1H), 7.69 (d, 1H), 7.42-7.27 (envelope, 9H), 7.13 (m, 1H), 7.00 (m, 4H), 6.90 (dd, 1H), 6.76 (d,1H), 6.48 (s, 1H), 4.60 (s, 4H), 3.90 (s, 3H). MS (DCI/NH_3) m/e 483 $(M+H)^+$.

Example 205B

Methyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-{[N,N-dimethylaminothiocarbonyl]oxy}benzoate

The compound described in Example 205A was converted to the title compound by the method of Example 203A, except recrystallization from MeOH was used for the purification. ^1H NMR ($CDCl_3$) δ 7.90 (d, 1H), 7.42-7.22

(nvelope, 11H), 7.13 (m, 1H), 7.01 (m, 4H), 6.57 (s, 1H), 4.60 (d, 4H), 3.90 (s, 3H), 3.63 (s, 3H), 3.58 (s, 3H). MS (DCI/NH_3) m/e 587 $(M+H+NH_3)^+$.

Example 205C

Methyl 4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino}-2-{[N,N-dimethylaminocarbonyl]thio}benzoate

The compound described in Example 205B was converted to the title compound by the method described in the first paragraph of Example 203B, except this compound was purified by chromatography using 1:1 hexane-EtOAc. ^1H NMR ($CDCl_3$) δ 7.86 (d, 1H), 7.50 (dd, 1H), 7.42 (d,1H), 7.40-7.22 (envelope, 9H), 7.13 (m, 1H), 7.01 (m, 4H), 6.61 (s, 1H), 4.58 (d, 4H), 3.10, 3.00 (both v br s, total 6H). MS (DCI/NH_3) m/e 587 $(M+H+NH_3)^+$.

Example 205D

3-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino-6-carboxy-thiophenol

The compound described in Example 205C was converted to the title compound by the method described in Example 27D, except the reaction was heated under reflux for 2 hours instead of stirring at room temperature overnight. Purification by preparative HPLC was required (Rainin Dynamax-60A C18 column, using a gradient of 20-100% CH_3CN vs 0.1% TFA in water), yielding both the title compound and the disulfide (Example 206). ^1H NMR (DMSO-d_6) δ 8.88 (s,1H), 7.82 (d, 1H), 7.69 (d, 1H), 7.37, 7.25 (both m, total 10H), 7.13 (m, 1H), 6.98 (m, 4H), 4.60 (s, 2H), 4.57 (s, 2H). MS (FAB+) m/e 485 $(M+H)^+$. Anal calcd for $C_{28}H_{24}N_2O_4S$: C, 69.40; H, 4.99; N, 5.78. Found: C, 69.01; H, 4.79; N, 5.62.

Example 206

Bis(5-[N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl]amino-2-carboxyphenyl) disulfide

The title compound was isolated as a biproduct in the preparation of the compound resulting from Example 205D. ^1H NMR (DMSO-d_6) δ 9.03 (s, 2H), 7.86 (m, 4H), 7.50 (dd, 2H), 7.38 (m, 4H), 7.30-7.10 (envelope, 16H), 6.96 (m, 8H), 4.50 (s, 4H), 4.44 (s, 4H). MS (FAB+) m/e 967 $(M+H)^+$. Anal calcd for

$C_{56}H_{46}N_4O_8S_2 \cdot 0.50\ H_2O$: C, 68.91; H, 4.85; N, 5.74. Found: C, 68.82; H, 4.67; N, 5.53.

Example 207

1,2-Di(acetoxymethoxycarbonyl)-4-{[N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl]oxy}benzene

The compound described in Example 38B (635 mg, 1.28 mmol) was dissolved in diglyme (10 mL), then triethylamine (657 mg, 0.90 mL, 6.50 mmol) was added. After 30 minutes, tetrabutylammonium iodide (200 mg, 0.54 mmol) and bromomethyl acetate (1.0 g, 6.5 mmol) were added. The reaction was stirred under N_2 at 50-60 °C for 20 hours, then cooled and partitioned between water and EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography eluting with 7:3 hexane-EtOAc to afford 310 mg (38%) of the title compound as a tacky solid. ^1H NMR ($CDCl_3$) δ 7.83 (d, 1H), 7.53, 7.37, 7.27, 7.13, 7.01 (all m, total 16H), 5.95 (s, 4H), 4.75 (m, 4H), 2.08, 2.07 (both s, total 6H). MS (FAB+) m/e 642 $(M+H)^+$. Anal calcd for $C_{35}H_{31}NO_{11}$: C, 65.52; H, 4.87; N, 2.18. Found: C, 65.22; H, 4.56; N, 1.92.

Example 208

5-{N-(2-Ethoxybenzyl)-N-[3-(3,4-dichlorophenoxy)benzyl]aminocarbonyl}-benzene-1,2,4-tricarboxylic acid

N-2-Ethoxybenzyl-N-[3-(3,4-dichlorophenoxy)benzyl]amine was prepared using the same procedure as given for the preparation for N-benzyl-N-(4-phenoxybenzyl) amine except replacing the benzyl amine with 2-ethoxybenzyl amine and the 4-phenoxybenzaldehyde with 3-(3,4-dichlorophenoxy)benzaldehyde.

The title compound was prepared by the procedures described in Example 148 using N-(2-ethoxybenzyl)-N-[3-(3,4-dichlorophenoxy)benzyl]-amine in place of N-benzyl-N-(4-phenoxy)benzylamine. ^1H NMR (DMSO-d_6, 300 MHz), δ 1.20 (dt, 3H), 3.90 (dq, 2H), 4.25 (d, 2H), 4.65 (s,2H), 6.80 - 7.65 (m, 11H), 7.70 (m, 1H), 8.40 (m, 1H). MS $(FAB)^+$ m/e 639 $(M+H)^+$ and $(FAB)^-$ m/e 637 $(M-H)^-$.

Example 209

5-{N-Benzyl-N-(3-chloro-4-phenoxy)benzylaminocarbonyl}benzene-1,2,4-tricarboxylic acid

N-Benzyl-N-(4-phenoxy-2-chlorobenzyl)amine was prepared using the same procedure as given for the preparation for N-benzyl-N-(4-phenoxybenzyl) amine except replacing the 4-phenoxybenzaldehyde with 4-phenoxy-2-chlorobenzaldehyde.

The title compound was prepared by the procedures described in Example 148 using N-benzyl-N-(4-phenoxy-3-chlorobenzyl)amine in place of N-2-ethoxybenzyl-N-[3-(4-methylphenoxy)benzyl] amine . ^{1}H NMR (DMSO-d_6, 300 MHz), δ 4.30 (d, 2H), 4.70 (b,2H), 6.80 - 7.45 (m, 13H), 7.80 (s, 1H), 8.35 (d, 1H). MS (FAB)$^+$ m/e 560 (M+H)$^+$ and (FAB)$^-$ m/e 558 (M-H)$^-$.

Example 210

2-Amino-5-{N-benzyl-N-(4-phenoxy)benzylaminocarbonylmethyl}benzene-1,4-dicarboxylic acid

Example 210A

Dimethyl 2-amino-5-allylterephthalate

The method described in Example 180B was used to convert allyltributyltin (9.93 g, 30 mmol) and the bromide resulting from Example 186A (8.07 g, 28.0 mmol) to the title compound (6.35 g, 91 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.14 (s, 1H), 5.97 (m, 1H), 5.64 (br s, 2H), 4.98 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 (dt, 2H).

Example 210B

2-Allyl-5-benzyloxycarbonylamino-4-benzyloxycarbonylbenzoic acid methyl ester

A solution of the compound resulting from Example 210A (4.72 g, 18.9 mmol), benzyl chloroformate (8.10 mL, 56.7 mmol) and N,N–diisopropylethylamine (7.34 g, 56.7 mmol) in dioxane (70 mL) was refluxed for 15 hours. After cooling to room temperature, the reaction mixture was diluted with ether and hexane (25 mL each), filtered through silica gel (100 g), and rinsed with dichloromethane and ether (1:1 mixture). The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography eluting with 15% ethyl acetate in hexane to give the title compound (8.11 g, 81%) mixed with an inseparable impurity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (br s, 1H), 8.93 (s, 1H), 7.93 (s, 1H), 7.40 (m, 10H), 5.96 (m, 1H), 5.36 (s, 2H), 5.22 (s, 2H), 5.01 (m, 2H), , 1H), 3.89 (s, 3H), 3.66 (dt, 2H).

Example 210C

2-{N-benzyl-N-(4-phenoxy)benzylaminocarbonylmethyl}-5-benzyloxycarbonylamino-4-benzyloxycarbonylbenzoic acid methyl ester

A mixture of the compound resulting from Example 210B (5.51 g, 12.0 mmol), ruthenium dioxide (113 mg, 0.85 mmol) and sodium periodate (921.8 g, 102 mmol) in acetonitrile (20 mL), carbon tetrachloride (20 mL) and water (30 mL) was heated at 55 °C for 3 hours. The mixture was then allowed to cool to room temperature, filtered through Celite, and rinsed with water (30 mL) and ethyl acetate (150 mL). The organic phase of the filtrate was separated, washed with 10% aqueous sodium bisulfite (40 mL), water (40 mL) and brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.

To the residue thus obtained and dissolved in dichloromethane (100 mL) was added N–benzyl-N-(4-phenoxy)benzylamine (4.95 g, 17.1 mmol), 4-dimethylaminopyridine (100 mg), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (3.26 g, 17.1 mmol). After 15 hours at room temperature, the reaction mixture was diluted with ether (200 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.

The residue was then purified by column chromatography eluting with 20% followed by 30% ethyl acetate in hexane to give the title compound (2.73 g, 3.65 mmol, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 9.08, 9.07 (2 s's, 1H), 7.89,7.86 (2s's, 1H), 7.44-6.90 (m, 24H), 5.34,5.33 (2 s's, 2H), 5.24 (s, 2H), 4.61, 4.60, 4.58, 4.56 (4 s's, 4H), 4.12, 4.09 (2 s's, 2H), 3.86, 3.85 (2 s's, 3H).

Example 210D

2-Amino-5-{N-benzyl-N-(4-phenoxy)benzylaminocarbonylmethyl}-4-methoxycarbonylbenzoic acid

A mixture of the amide resulting from Example 210C (2.47 g, 3.30 mmol) and 10% palladium on carbon (1 g) in methanol (30 mL) was stirred under a hydrogen balloon for 4 hours. The mixture was then filtered through Celite, rinsed with methanol, and concentrated *in vacuo* to give the title compound (1.59 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58, 7.55 (2 s, 1H), 7.43-7.20 (m, 10H), 7.14 (m, 1H), 6.98 (m, 4H), 4.62, 4.58 (2 s, 2H), 4.47, 4.45 (2 s, 2H), 4.01, 3.97 (2 s, 2H), 3.71,3.70 (2 s, 3H). MS (FAB$^+$) m/e 525 $(M+H)^+$.

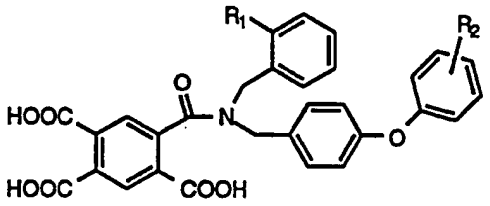
Example 210E

2-Amino-5-{N-benzyl-N-(4-phenoxy)benzylaminocarbonylmethyl}benzene-1,4-dicarboxylic acid

The method described in Example 173B was used to convert the compound resulting from Example 210D (221 mg, 0.42 mmol) to the title compound (212 mg, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.63, 7.60 (2 s, 1H), 7.50-7.17 (m, 11H), 7.13 (m, 4H), 4.65, 4.62 (2 s, 2H), 4.53, 4.51 (2 s, 2H), 4.08, 4.04 (2 s, 2H). MS (FAB$^+$) m/e 511 $(M+H)^+$.

Examples 211-345

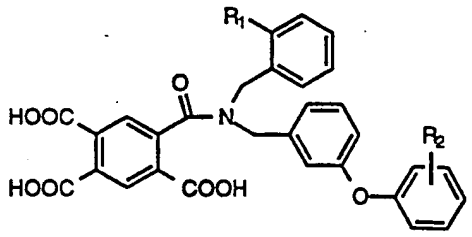
Using the procedures described in the schemes and preceeding examples, the following compounds can be prepared:



Example No.	R_1	R_2
211	H	4-CF_3
212	H	4-Cl
213	H	4-F
214	H	3-Br
215	H	4-$PhCH_2$
216	H	3-Cl, 4-Cl
217	H	3-CF_3
218	H	3-Cl
219	H	3-F
220	H	3-Br
221	CH_3CH_2O	4-CH_3
222	CH_3CH_2O	4-CF_3
223	CH_3CH_2O	4-Cl
224	CH_3CH_2O	4-F
225	CH_3CH_2O	3-Br
226	CH_3CH_2O	3-Cl, 4-Cl
227	CH_3CH_2O	3-CH_3
228	CH_3CH_2O	3-CF_3
229	CH_3CH_2O	3-Cl
230	CH_3CH_2O	3-F
231	CH_3CH_2O	3-Br
232	CH_3O	4-CH_3

233	CH_3O	4-CF_3
234	CH_3O	4-Cl
235	CH_3O	4-F
236	CH_3O	3-Br
237	CH_3O	4-$PhCH_2$
238	CH_3O	3-Cl, 4-Cl
239	CH_3O	3-CH_3
240	CH_3O	3-CF_3
241	CH_3O	3-Cl
242	CH_3O	3-F
243	CH_3O	3-Br
244	$(CH_3)_2CH(CH_2)_2O$	4-CH_3
245	$(CH_3)_2CH(CH_2)_2O$	4-CF_3
246	$(CH_3)_2CH(CH_2)_2O$	4-Cl
247	$(CH_3)_2CH(CH_2)_2O$	4-F
248	$(CH_3)_2CH(CH_2)_2O$	3-Br
249	$(CH_3)_2CH(CH_2)_2O$	4-$PhCH_2$
250	$(CH_3)_2CH(CH_2)_2O$	3-Cl, 4-Cl
252	$(CH_3)_2CH(CH_2)_2O$	3-CH_3
252	$(CH_3)_2CH(CH_2)_2O$	3-CF_3
253	$(CH_3)_2CH(CH_2)_2O$	3-Cl
254	$(CH_3)_2CH(CH_2)_2O$	3-F
255	$(CH_3)_2CH(CH_2)_2O$	3-Br
256	$CH_3(CH_2)_5O$	4-CH_3
257	$CH_3(CH_2)_5O$	4-CF_3
258	$CH_3(CH_2)_5O$	4-Cl
259	$CH_3(CH_2)_5O$	4-F
260	$CH_3(CH_2)_5O$	3-Br
261	$CH_3(CH_2)_5O$	4-$PhCH_2$
262	$CH_3(CH_2)_5O$	3-Cl, 4-Cl
263	$CH_3(CH_2)_5O$	3-CH_3
264	$CH_3(CH_2)_5O$	3-CF_3
265	$CH_3(CH_2)_5O$	3-Cl

266	$CH_3(CH_2)_5O$	3-F
267	$CH_3(CH_2)_5O$	3-Br
268	2-Ph-O	4-CH_3
269	2-Ph-O	4-CF_3
270	2-Ph-O	4-Cl
271	2-Ph-O	4-F
272	2-Ph-O	3-Br
273	2-Ph-O	4-$PhCH_2$
274	2-Ph-O	3-Cl, 4-Cl
275	2-Ph-O	3-CH_3
276	2-Ph-O	3-CF_3
277	2-Ph-O	3-Cl
278	2-Ph-O	3-F
279	2-Ph-O	3-Br

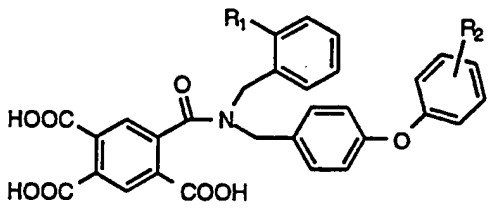


Example No.	R_1	R_2
280	H	4-CF_3
281	H	4-F
282	H	3-Br
283	H	4-$PhCH_2$
284	H	3-Cl, 4-Cl
285	H	3-CH_3
286	H	3-CF_3
287	H	3-Cl
288	H	3-F

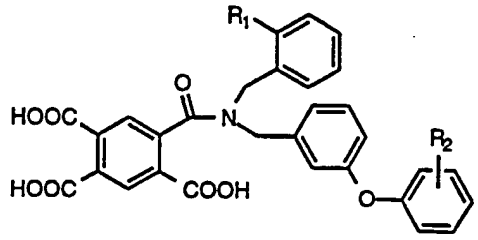
289	H	3-Br
290	CH_3CH_2O	4-CF_3
291	CH_3CH_2O	4-F
292	CH_3CH_2O	3-Br
293	CH_3CH_2O	4-$PhCH_2$
294	CH_3CH_2O	3-CH_3
295	CH_3CH_2O	3-CF_3
296	CH_3CH_2O	3-Cl
297	CH_3CH_2O	3-F
298	CH_3CH_2O	3-Br
299	CH_3O	4-CF_3
300	CH_3O	4-Cl
301	CH_3O	4-F
302	CH_3O	3-Br
303	CH_3O	4-$PhCH_2$
304	CH_3O	3-Cl, 4-Cl
305	CH_3O	3-CH_3
306	CH_3O	3-CF_3
307	CH_3O	3-Cl
308	CH_3O	3-F
309	CH_3O	3-Br
310	$(CH_3)_2CH(CH_2)_2O$	4-CH_3
311	$(CH_3)_2CH(CH_2)_2O$	4-CF_3
312	$(CH_3)_2CH(CH_2)_2O$	4-Cl
313	$(CH_3)_2CH(CH_2)_2O$	4-F
314	$(CH_3)_2CH(CH_2)_2O$	3-Br
315	$(CH_3)_2CH(CH_2)_2O$	4-$PhCH_2$
316	$(CH_3)_2CH(CH_2)_2O$	3-Cl, 4-Cl
317	$(CH_3)_2CH(CH_2)_2O$	3-CH_3
318	$(CH_3)_2CH(CH_2)_2O$	3-CF_3
319	$(CH_3)_2CH(CH_2)_2O$	3-Cl
320	$(CH_3)_2CH(CH_2)_2O$	3-F
321	$(CH_3)_2CH(CH_2)_2O$	3-Br

322	$CH_3(CH_2)_5O$	4-CH_3
323	$CH_3(CH_2)_5O$	4-CF_3
324	$CH_3(CH_2)_5O$	4-Cl
325	$CH_3(CH_2)_5O$	4-F
326	$CH_3(CH_2)_5O$	3-Br
327	$CH_3(CH_2)_5O$	4-$PhCH_2$
328	$CH_3(CH_2)_5O$	3-Cl, 4-Cl
329	$CH_3(CH_2)_5O$	3-CH_3
330	$CH_3(CH_2)_5O$	3-CF_3
331	$CH_3(CH_2)_5O$	3-Cl
332	$CH_3(CH_2)_5O$	3-F
333	$CH_3(CH_2)_5O$	3-Br
334	2-Ph-O	4-CH_3
335	2-Ph-O	4-CF_3
336	2-Ph-O	4-Cl
337	2-Ph-O	4-F
338	2-Ph-O	3-Br
339	2-Ph-O	4-$PhCH_2$
340	2-Ph-O	3-Cl, 4-Cl
341	2-Ph-O	3-CH_3
342	2-Ph-O	3-CF_3
343	2-Ph-O	3-Cl
344	2-Ph-O	3-F
345	2-Ph-O	3-Br

Using the procedures described in the schemes and preceeding examples, the following compounds can be prepared:



or

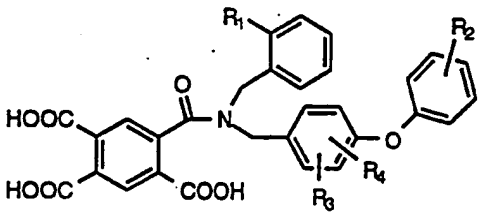


wherein

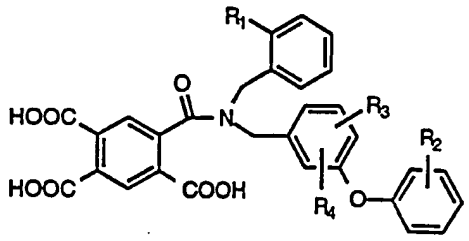
R_1 is selected from the group consisting of nitro, hydroxy, ethyl, amino, methylamino, carboxy, methoxycarbonyl, ethoxycarbonyl, pentafluoroethoxy, methoxy, ethoxy, n-hexyloxy, cyano, carboxamido, fluoro, bromo, chloro, and iodo; and

R_2 is selected from the group consisting of 4-methyl, 4-iodo, 4-chloro, 4-fluoro, 4-ethyl, 4-trifluoromethyl, 3,4-dichloro, 3,5-dichloro, 4-isopropyl, 3,4-diiodo, 3,5-diiodo, 3,4-difluoro, 3,5-difluoro, and 3,4,5-trifluoro.

Using the procedures described in the schemes and preceeding examples, the following compounds can be prepared:



or



wherein

R_1 is selected from the group consisting of nitro, hydroxy, ethyl, amino, methylamino, carboxy, methoxycarbonyl, ethoxycarbonyl, pentafluoroethoxy, methoxy, ethoxy, n-hexyloxy, cyano, carboxamido, fluoro, bromo, chloro, and iodo;

R_2 is selected from the group consisting of 4-methyl, 4-iodo, 4-chloro, 4-fluoro, 4-ethyl, 4-trifluoromethyl, 3,4-dichloro, 3,5-dichloro, 4-isopropyl, 3,4-diiodo, 3,5-diiodo, 3,4-difluoro, 3,5-difluoro, and 3,4,5-trifluoro; and

R_3 and R_4 are each independently selected from the group consisting of hydrogen, chloro, bromo, iodo, fluoro, methyl, methoxy, dichloro, difluoro, diiodo, and dimethyl.

Inhibition of Protein Farnesyltransferase

In vitro inhibition of protein farnesyltransferase can be measured by the following procedure. (Procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States patent No. 5245061.)

Rat brain protein farnesyltransferase activity was measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO_2H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme used is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at 1×10^{-5} M) compared to an uninhibited control sample was evaluated in the same Amersham test system. The results for the compounds of the invention are shown in Table 1. The data show that the compounds of the invention are inhibitors of protein farnesyltransferase.

Table 1

In vitro Inhibition of Protein Farnesyltransferase

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM
1	99	2	95
3	88	5	53
6	41	7	70
8	98	9	87
10	86	11	84
14	41	16	57
18	54	19	98
20	82	21	67
22	87	23	66
24	71	25	52
26	61	27	57
28	61	29	97
30	89	31	79
33	43	34	87
35	71	36	91
37	93	38	95
39	96	40	81
41	86	42	96
43	73	44	70
45	97	46	87
47	92	48	96
49	95	50	95
51	96	52	98
53	96	54	78
55	44	56	80
58	24	60	63

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM
61	92	63	40
64	31	66	65
67	90	68	74
69	23	70	95
71	27	72	96
73	81	74a	66
74b	86	75	69
77	48	82	57
84	70	86	38
88	25	89	23
91	71	92	79
93	97	94	92
95	93	97	69
98	66	100	81
101	42	102a	38
102b	76	103	94
105	97	106	94
108	94	109	93
112	96	113	32
114	29	115	37
116	39	118	89
119	72	120	91
121b	63	122	46
123	60	124	35
126b	44	129	91
130	98	131	93
132	57	133	82
134	39	135	98

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM (* at 0.01 μM)
136	86	137	99
138	98	139	97
140	97	141	92
143	98	144	76
145	87	146	91
147	93	148	98
149	94	150	82*
151	93	152	99
153	97	154	62
155	48	156	82
157	60	159	34
159	34	160	77
161	43	162	72
163	89	164	81
165	71	166	61
167	63	169	96
170	31	171	98
172	71	173	42
174	68	175	69
176	46	177	43
178	54	179	78
180	90	181	92
183	87	185	76
186	58	187	98
188	74	189	98
190	93	191	49
192	87	193	70
194	95	196	97
198	96	199	64
200	98	210	78

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the

like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein farnesyltransferase and the farnesylation of Ras. These inhibitors of protein farnesyltransferase are also useful for inhibiting or treating cancer in humans and other mammals. Examples of the kinds of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas, such as lung, colorectal, exocrine pancreatic, cervical, esophageal, stomach, and small intestinal; sarcomas, such as oesteroma, osteosarcoma, lepoma, liposarcoma, hemanioma, and hemangiosarcoma; melanomas, such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma andHodgkins disease; and leukemias, such as myeloid, acute lymphoblastic, chronic lymphocytic, acute myloblastic and chronic mylocytic.

The ability of the compounds of the invention to inhibit or treat carcinoma can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., Drugs Exptl. Clin. Res. 13(6), 345-351 (1987); Bissery, MC, Guenard F, Guerritte-Voegelein F, Lavelle F., Cancer Res. 51, 4845-4852 (1991); and Rygaard J, and Povlsen C., Acta Pathol. Microbiol. Scand. 77, 758 (1969).

These inhibitors of protein farnesyltransferase are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. Circ. Res. 73: 264-268 (1993), Mitsuka, M. et al. Circ. Res. 73: 269-275 (1993) and Santoian, E.C. et al. Circulation 88: 11-14 (1993).

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described inHolleb, et al., Clinical Oncology, American Cancer Society, United States (1991) p 56 et seq. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethyenimines (thiotepa, hexamethylmelamine); folic acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside); purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine, vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin, taxol, brequinar).

The above compounds to be employed in combination with the farnesyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

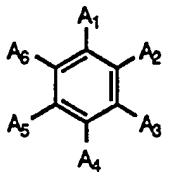
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

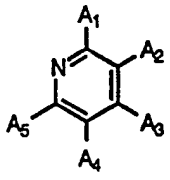
CLAIMS

What is claimed is:

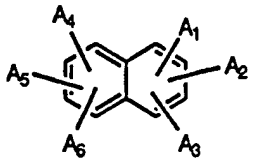
1. A compound of the formula



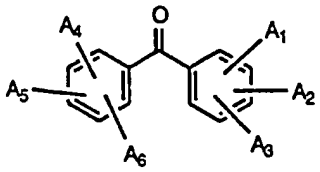
(I),



(II),



(III) or



(IV)

wherein

A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from the group consisting of

(1) hydrogen;
(2) halogen;
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) -X-T-G

wherein at each occurrence T is independently selected from the group consisting of

a) a covalent bond,
b) -C(O)-,

c) -C(S)- and
d) $-S(O)_2-$,

at each occurrence X is independently selected from the group consisting of
a) a covalent bond,
b) $-CH_2-$,
c) -O-,
d) -S- and
e) $-N(R_a)-$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl,

and at each occurrence G is independently selected from the group consisting of
a) R_2 ,
b) $-N(R_1)(R_2)$
wherein at each occurrence R_1 is independently selected from the group consisting of
(i) $-CH(R_d)C(O)OR_e$ wherein at each occurrence R_d is independently selected from the group consisting of loweralkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, thioalkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, arylalkyl and alkylsulfonylalkyl and at each occurrence R_e is independently selected from the group consisting of hydrogen and carboxy-protecting group,
(ii) aryl,
(iii) arylalkyl,
(iv) heterocyclic,
(v) (heterocyclic)alkyl,
(vi) cycloalkylalkyl and
(vii) aryl, heterocyclic, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the aryl part of the arylalkyl group, the heterocyclic group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with one or two

substituents -W-R_4 wherein at each occurrence W is independently selected from the group consisting of (a) a covalent bond, (b) -C(O)-, (c) -CH_2-, (d) -O-, (e) -$S(O)_p$- wherein p is 0, 1 or 2, (f) -$N(R_c)$- wherein R_c is hydrogen or loweralkyl, (g) -CH_2O-, (h) -$CH_2S(O)_p$- wherein p is 0, 1 or 2 and (i) -$CH_2N(R_c)$- wherein R_c is hydrogen or loweralkyl and

at each occurrence R_4 is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl,

and

at each occurrence R_2 is independently selected from the group consisting of

(i) aryl,
(ii) arylalkyl,
(iii) alkenyl,
(iv) alkynyl,
(v) arylalkenyl,
(vi) arylalkynyl,
(vii) (heterocyclic)alkyl,
(viii) aryloxyalkyl,
(ix) aryloxyalkenyl,
(x) arylalkoxyalkenyl,
(xi) arylalkyl wherein the alkyl group is substituted with (a) -OR_{10} wherein R_{10} is hydrogen or alkanoyl or (b) -$C(O)OR_h$ wherein R_h is hydrogen or a carboxy-protecting group,
(xii) aroyloxyalkyl, and
(xiii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is

substituted with one or two substituents -Y-R_3 wherein at each occurrence Y is independently selected from the group consisting of (a) a covalent bond, (b) -C(O)-, (c) -CH_2-, (d) -O-, (e) -$S(O)_m$- wherein m is 0, 1 or 2, (f) -$N(R_b)$- wherein R_b is hydrogen or loweralkyl, (g) -CH_2O-, (h) -$CH_2S(O)_m$- wherein m is 0, 1 or 2 and (i) -$CH_2N(R_b)$- wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl,

and

c) -NHR_{2a} or -OR_{2a}
wherein at each occurrence R_{2a} is independently selected from the group consisting of

(i) arylalkyl and

(ii) heterocyclicalkyl,

wherein the alkyl part of the arylalkyl group or the heterocyclicalkyl group is substituted with an arylalkyl group and wherein the aryl part of the arylalkyl group or the heterocyclic part of the heterocyclicalkyl group is substituted with one or two substituents -Y'-$R_{3'}$ wherein at each occurrence Y' is independently selected from the group consisting of (a) a covalent bond, (b) -C(O)-, (c) -CH_2-, (d) -O-, (e) -$S(O)_{m'}$- wherein m' is 0, 1 or 2, (f) -$N(R_{b'})$- wherein $R_{b'}$ is hydrogen or loweralkyl, (g) -CH_2O-, (h) -$CH_2S(O)_{m'}$- wherein m' is 0, 1 or 2 and (i) -$CH_2N(R_{b'})$- wherein $R_{b'}$ is hydrogen or loweralkyl and at each occurrence $R_{3'}$ is independently selected from the group consisting of (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;

(7) -Z wherein at each occurrence Z is independently selected from the group consisting of

a) -Q-D

wherein at each occurrence D is independently selected from the group consisting of

(i) $-C(O)R_6$ wherein at each occurrence R_6 is independently selected from the group consisting of hydrogen and a carboxy-protecting group,

(ii) -C(O)H,

(iii) $-CH_2OH$,

(iv) $-C(O)CF_3$,

(v) $-CH(OH)CF_3$,

(vi) $-C(OH)(CF_3)_2$,

(vii) $-C(O)NH_2$,

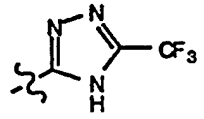
(viii) -C(O)NHOH,

(ix) -CH(=NOH),

(x) $-S(O)_2NH_2$,

(xi) $-NHS(O)_2CH_3$ or $-NHS(O)_2CF_3$,

(xii) 5-tetrazolyl,

(xiii) 

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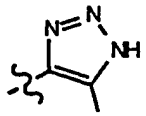
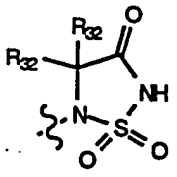
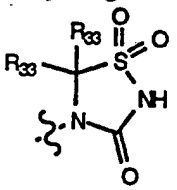
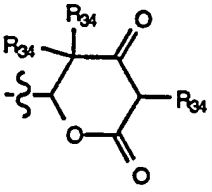
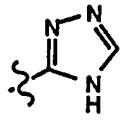


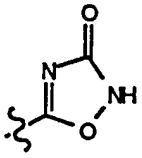
(xiv) R_{30} wherein R_{30} is -CN, $-NO_2$, or $-CO_2R_{31}$ wherein R_{31} is hydrogen, aryl or loweralkyl,

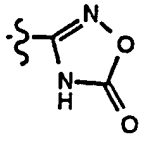
(xv)  wherein at each occurrence R_{32} is independently selected from the group consisting of hydrogen and loweralkyl,

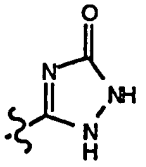
(xvi)  wherein at each occurrence R_{33} is independently selected from the group consisting of hydrogen and loweralkyl,

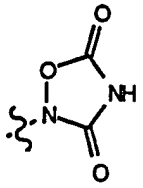
(xvii)  wherein at each occurrence R_{34} is independently selected from the group consisting of hydrogen, loweralkyl, alkenyl, alkoxyalkyl and benzyl,

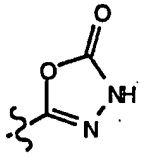
(xviii)  ,

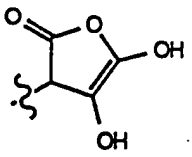
(xix)  ,

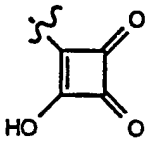
(xx)  ,

(xxi)  ,

(xxii)  ,

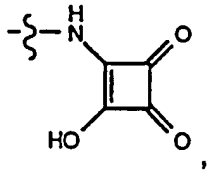
(xxiii)  ,

(xxiv)  ,

(xxv)  ,

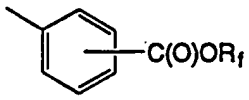
and

wherein at each occurrence Q is independently selected from the group consisting of (i) a covalent bond, (ii) $-OCH_2-$, (iii) alkylene, and (iv) alkenylene;

b)  ,

and

c)



wherein at each occurrence R_f is independently selected from the group consisting of hydrogen and a carboxy-protecting group;

(8) $-C(O)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above;

(9) $-CH(OH)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above;

(10) $-CH=C(R_{2b})(R_{2c})$ wherein at each occurrence R_{2b} is independently selected from arylalkyl and at each occurrence R_{2c} is independently selected from the group consisting of aryl and heterocyclic wherein the aryl or heterocyclic ring is subsubstituted with $-Y'-R_{3'}$ wherein at each occurrence Y' and $R_{3'}$ are independently defined as above,

(11) $-C(O)-CH(R_{2a})CH(R_{2d})C(O)OR_g$ wherein at each occurrence R_{2a} is independently defined as above, at each occurrence R_{2d} is independently selected from aryl and at each occurrence R_g is independently selected from the group consisting of hydrogen and a carboxy-protecting group;

and

(12) -C(O)NH(arylalkyl);

or any two adjacent substituents selected from A_1, A_2, A_3, A_4, A_5 and A_6 taken together form a 5-, 6- or 7-membered cyclic anhydride group;

with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is independently selected from the group consisting of
(1) -X-T-G wherein at each occurrence X, T and G are independently defined as above,
(2) $-C(O)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above,
(3) $-CH(OH)R_{2a}$ wherein at each occurrence R_{2a} is independently defined as above,
(4) $-CH=C(R_{2b})(R_{2c})$ wherein at each occurrence R_{2b} and R_{2c} are independently defined as above,
and
(5) $-C(O)-CH(R_{2a})CH(R_{2d})C(O)OR_g$ wherein at each occurrence R_{2a}, R_{2d} and R_g are independently defined as above,

and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is -Z which at each occurrence is independently defined as above;

or a pharmaceutically acceptable salt thereof.

2. A compound as defined by Claim 1 wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from
(1) hydrogen,
(2) halogen,
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) heterocyclic, (iv) (heterocyclic)alkyl and (vi) R_2, and at each occurrence R_2 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) alkenyl,

(iv) alkynyl, (v) arylalkenyl, (vi) arylalkynyl, (vii) (heterocyclic)alkyl, (viii) aryloxyalkyl, (ix) aryloxyalkenyl, (x) arylalkoxyalkenyl, (xi) arylalkyl wherein the alkyl group is substituted with $-OR_{10}$ wherein R_{10} is hydrogen or alkanoyl, and (xii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with $-Y-R_3$ wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) $-C(O)-$, (c) $-CH_2-$, (d) $-O-$, (e) $-S(O)_m-$ wherein m is 0, 1 or 2, (f) $-N(R_b)-$ wherein R_b is hydrogen or loweralkyl, (g) $-CH_2O-$, (h) $-CH_2S(O)_m-$ wherein m is 0, 1 or 2 and (i) $-CH_2N(R_b)-$ wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;

and

(7) $-Q-C(O)R_6$ wherein at each occurrence Q is independently selected from (a) a covalent bond, (b) alkylene, and (c) alkenylene and R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;

with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-Q-C(O)R_6$ wherein Q and R_6 are as defined above.

3. A compound as defined by Claim 1 of the formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from

(1) hydrogen,

(2) halogen,

(3) loweralkyl;

(4) hydroxy;

(5) alkoxy;

(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or

$-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) heterocyclic, (iv) (heterocyclic)alkyl and (vi) R_2, and at each occurrence R_2 is independently selected from the group consisting of (i) aryl, (ii) arylalkyl, (iii) alkenyl, (iv) alkynyl, (v) arylalkenyl, (vi) arylalkynyl, (vii) (heterocyclic)alkyl, (viii) aryloxyalkyl, (ix) aryloxyalkenyl, (x) arylalkoxyalkenyl, (xi) arylalkyl wherein the alkyl group is substituted with $-OR_{10}$ wherein R_{10} is hydrogen or alkanoyl, and (xii) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with $-Y-R_3$ wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) $-C(O)-$, (c) $-CH_2-$, (d) $-O-$, (e) $-S(O)_m-$ wherein m is 0, 1 or 2, (f) $-N(R_b)-$ wherein R_b is hydrogen or loweralkyl, (g) $-CH_2O-$, (h) $-CH_2S(O)_m-$ wherein m is 0, 1 or 2 and (i) $-CH_2N(R_b)-$ wherein R_b is hydrogen or loweralkyl and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) cycloalkyl, (d) cycloalkylalkyl, (e) heterocyclic and (f) (heterocyclic)alkyl;

and

(7) $-Q-C(O)R_6$ wherein at each occurrence Q is independently selected from (a) a covalent bond, (b) alkylene, and (c) alkenylene and R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;

with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-Q-C(O)R_6$ wherein Q and R_6 are as defined above.

4. A compound as defined by Claim 1 of formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from

(1) hydrogen,

(2) halogen,

(3) loweralkyl;

(4) hydroxy;
(5) alkoxy;
(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from (i) arylalkyl, (ii) (heterocyclic)alkyl and (iii) R_2, and at each occurrence R_2 is independently selected from (i) arylalkyl, (ii) arylalkenyl, (iii) aryloxyalkyl, (iv) aryloxyalkenyl, (v) arylalkoxyalkenyl, and (vi) aryl, arylalkyl or (heterocyclic)alkyl wherein the aryl group, the the aryl part of the arylalkyl group or the heterocyclic part of the (heterocyclic)alkyl group is substituted with $-Y-R_3$ wherein at each occurrence Y is independently selected from (a) a covalent bond, (b) $-CH_2-$, and (c) -O- and at each occurrence R_3 is independently selected from (a) aryl, (b) arylalkyl, (c) heterocyclic and (d) (heterocyclic)alkyl;
and
(7) $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;
with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)R_6$ wherein R_6 is as defined above.

5. A compound as defined by Claim 1 of formula (I) wherein A_1, A_2, A_3, A_4, A_5 and A_6 are independently selected from
(1) hydrogen,
(2) halogen,
(3) loweralkyl;
(4) hydroxy;
(5) alkoxy;
(6) $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$

wherein at each occurrence R_1 is independently selected from benzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl and 4-(phenoxy)phenethyl;
and
(7) $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group;
with the proviso that one or two of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 and R_2 are as defined above, and with the proviso that one, two or three of A_1, A_2, A_3, A_4, A_5 and A_6 is $-C(O)R_6$ wherein R_6 is as defined above.

6. A compound as defined by Claim 1 of formula (I) wherein A_1 is $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein R_1 is selected from benzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and R_2 is selected from 4-(phenoxy)benzyl and 4-(phenoxy)phenethyl;
A_2, A_4 and A_5 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; or A_3 and A_4 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; or A_2 and A_4 are $-C(O)R_6$ wherein R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen.

7. A compound as defined by Claim 1 of formula (I) wherein A_1 and A_4 are $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or

$-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from benzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl and 4-(phenoxy)phenethyl; and A_2 and A_5 are R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen;

or A_1 and A_5 are $-C(O)NR_1R_2$, $-N(R_a)-C(O)NR_1R_2$ wherein R_a is hydrogen, loweralkyl, cycloalkyl, cycloalkylalkyl or arylalkyl, $-O-C(O)NR_1R_2$ or $-CH_2-C(O)NR_1R_2$ wherein at each occurrence R_1 is independently selected from benzyl, chlorobenzyl, dichlorobenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl and 4-(phenoxy)benzyl, and at each occurrence R_2 is independently selected from 4-(phenoxy)benzyl and 4-(phenoxy)phenethyl; and A_2 and A_4 are R_6 is $-OR_7$ wherein at each occurrence R_7 is independently hydrogen or a carboxy-protecting group; and the remaining members of the group A_1, A_2, A_3, A_4, A_5 and A_6 are hydrogen.

8. A compound selected from the group consisting of:

5-(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)benzene-1,2,4-tricarboxylic acid;

2,5-Di(N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl) benzene-1,4-dicarboxylic acid;

4,6-Di(N-benzyl-N-(4-phenoxybenzyl)aminocarbonyl) benzene-1,3-dicarboxylic acid;

5-(N-Phenethyl-N-(4-phenoxybenzyl)diaminocarbonyl)benzene-1,2,4-tricarboxylic acid;

4-(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)benzene-1,2-dicarboxylic acid;

5-(N,N-Di(4-phenoxybenzyl)aminocarbonyl)benzene-1,2,4-tricarboxylic acid;

5-(N-(4-Phenoxybenzyl)-N-(4-phenylbutyl)aminocarbonyl)-benzene-1,2,4-tricarboxylic acid;

5-(N-(3,4-Dichlorobenzyl)-N-(4-phenoxybenzyl)aminocarbonyl)-benzene-1,2,4-tricarboxylic acid;

4-(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)benzene-1,3-dicarboxylic acid;

5-(N-Benzyl-N-(2-(4-phenoxyphenyl)ethyl)aminocarbonyl)-benzene-1,2,4-tricarboxylic acid;

4-{(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)amino}benzene-1,2-dicarboxylic acid;

4-{(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)oxy}benzene-1,2-dicarboxylic acid;

4-{(N-Benzyl-N-(4-phenoxybenzyl)aminocarbonyl)methyl}-1,2-benzene dicarboxylic acid; and

5-[N-(2-Ethoxybenzyl)-N-(3-(4-methylphenoxy)benzyl)aminocarbonyl]-benzene-1,2,4-tricarboxylic acid;

or a pharmaceutically acceptable salt thereof.

9. 5-[N-(2-Ethoxybenzyl)-N-(3-(4-methylphenoxy)benzyl)-aminocarbonyl]-benzene-1,2,4-tricarboxylic acid,
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for inhibiting protein farnesyltransferase comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

11. A method for inhibiting farnesylation of Ras protein in a human or lower mammal in need of such treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.

12. A method for inhibiting or treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 1.

13. A method for inhibiting or treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 1 in combination with one or more chemotherapeutic agents.

14. A method for preventing restenosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 1.

15. A pharmaceutical composition for inhibiting protein farnesyltransferase comprising a therapeutically effective amount of a compound according to Claim 7 and a pharmaceutically acceptable carrier.

16. A method for inhibiting farnesylation of Ras protein in a human or lower mammal in need of such treatment comprising administering a therapeutically effective amount of a compound according to Claim 8.

17. A method for inhibiting or treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 8.

18. A method for inhibiting or treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 8 in combination with one or more chemotherapeutic agents.

19. A method for preventing restenosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 8.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/06193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/73 C07C233/65 C07C235/38 C07D257/04 C07C275/42
C07C335/22 C07C233/12 C07D333/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 387 106 (DEVRIES, VERN G. ET AL) 7 June 1983 see column 7, table I, last two compounds ---	1-4
P,A	WO,A,95 21815 (ABBOTT LAB) 17 August 1995 -----	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 1996	27. 09. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Seufert, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/06193

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12,13,17 and 18 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds/compositions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched incompletely: 1-4, 10-19

Please see attached sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INF RMATION C NTINUED FROM PCT/ISA/

The vast number of theoretically conceivable compounds resulting from the combination of the structures I, II, III and IV with all claimed substituents precludes a comprehensive search. For economic reasons the search had to be limited. Search and search report can be considered complete for compounds having the structure I, II, III and IV wherein at least one of A1, A2, A3, A4, A5 or A6 is a -C(O)NR1R2 or -N(Ra)C(O)NR1R" group and at least one of A1, A2, A3, A4, A5 or A6 is a C(O)OR7 group with R1 and R2 as defined in claims 5 - 9.

(cf. rule 33 PCT; Guidelines Exam. Part B, Chap. III, 3.6 and 3.7)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 96/06193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4387106	07-06-83	NONE	
WO-A-9521815	17-08-95	NONE	